

Haemostasis at open and laparoscopic myomectomy with the use of modified triple tourniquets

**MD Thesis
University of London**

A Alexander Taylor MB BS MRCOG

Honorary Lecturer in Obstetrics & Gynaecology
Royal Free Hospital
Royal Free and University College Medical School
London
UK

2005

UMI Number: U602468

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



UMI U602468

Published by ProQuest LLC 2014. Copyright in the Dissertation held by the Author.
Microform Edition © ProQuest LLC.

All rights reserved. This work is protected against
unauthorized copying under Title 17, United States Code.



ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Contents

Dedications	3
Abstract	4
Chapter One Introduction	6
Chapter Two Background to Thesis	25
Chapter Three Consultant Survey	30
Chapter Four Prospective randomised controlled trial of triple tourniquets at open myomectomy	45
Chapter Five A feasibility study of triple tourniquets at laparoscopy myomectomy	61
Chapter Six The effect of tourniquets on uterine blood flow	73
Chapter Seven The effect of tourniquets on ovarian function	89
Chapter Eight The effect of open myomectomy on menstrual blood loss	96
Chapter Nine Psycho-social and quality of life data after open myomectomy	102
Chapter Ten Summary	111
Chapter Eleven Future research	114
Appendices	
Appendix 1: References	118
Appendix 2: Forms	130
Appendix 3: CD (including movies and Excel files containing original data for the studies	139

This thesis is dedicated to the loving memory of my father a man who “was successful in combining scientific medicine and traditional family doctoring with a skill that belied his years”.

Abstract

Objectives

To investigate the prevalence of haemostatic techniques at myomectomy. To investigate the effectiveness of modified triple tourniquets at open myomectomy and for the first time to pilot their use at laparoscopic myomectomy.

Design

A questionnaire based postal survey.

A randomised controlled trial (RCT) and a feasibility study

Population

All UK Consultant Obstetricians & Gynaecologists.

38 patients with symptomatic fibroids undergoing open or laparoscopic myomectomy.

Methods

A standard questionnaire postal survey. At open myomectomy a number 1 polyglactin suture was tied around the cervix to occlude the uterine arteries, and polythene (polyglactin at laparoscopic myomectomy) tourniquets were tied around the ovarian vessels. At the end of the procedure the ovarian ties were released but the uterine artery suture remained *in situ*.

Outcome measures

Use of haemostatic techniques at open, laparoscopic and hysteroscopic myomectomy.

Intra-operative blood loss, post-operative blood loss, blood transfusion rates, operative morbidity, uterine blood flow, ovarian function, quality of life and effect on menstruation.

Results

59% responded to the survey. At open myomectomy 90% regularly used a haemostatic technique, with 85% prescribing pre-operative gonadotrophin releasing hormone agonists.

Open myomectomy RCT there was less blood lost in the tourniquet group than in the control ($p < 0.0001$). The volume in the pelvic drain postoperatively failed to reach statistical significance between the two groups. There were no differences in uterine artery Doppler resistance indices and ovarian function was unaffected by the tourniquets. Open myomectomy significantly improved menorrhagia and quality of life.

In the laparoscopic study triple tourniquets were applied successfully and appeared effective.

Conclusions

Modified triple tourniquets are effective in reducing bleeding at open myomectomy and appear safe with no obvious effect on uterine perfusion or ovarian function. Our feasibility study would suggest they can also be successfully used at laparoscopic myomectomy.

Chapter One: Introduction

Leiomyomas

Definition

Leiomyomas are benign smooth muscle tumours that arise from the clonal expansion of single myocytes ¹. They are associated with variable amounts of collagen and fibrous tissue and it is this pathological feature that has led them to being colloquially known as “fibroids” ². Throughout this thesis, the two terms will be used interchangeable.

Epidemiology and Aetiology

A review of the epidemiology of uterine fibroids reveals a wide variation in reported prevalence rates. The figures quoted reflect the different diagnostic tests used, populations studied and the differences in trial design. One of the seminal papers on fibroids reported a prevalence rate of 25% based on clinical examination ³, whilst others looking at the presence of myomas in hysterectomy specimens reported rates of 77% ⁴. The largest study to date, the Nurses' Health Study II, consisting of 116,678 female nurses aged 25-42 years, prospectively followed the group with questionnaires every two years, to determine the incidence of uterine leiomyoma among premenopausal woman both by age and race ⁵. The diagnosis of fibroids was self reported and confirmed for a sample of cases. The crude incidence rate in this study was 12.8 per 1000 woman years. However the age standardised rates were much higher in black women than in white women, 30.6 and 8.9 per 1000 woman years respectively. Even after adjusting for a number of variables such as body mass index, infertility and contraception, the rates among black

women were significantly higher than those amongst white women (relative risks 3.25; 95% CI 2.71-3.88). The incidence of fibroids amongst women of Hispanic or Asian ethnic origin in this study, were similar to those of white women.

Although the above study was a prospective longitudinal one and looked at large numbers of women, it might nonetheless have overestimated the risks because of detection bias. A more recent study from the National Institute of Environmental Health Sciences (NIEHS) aimed to obtain unbiased estimates of the age-specific cumulative incidence of uterine fibroids ⁶. This was achieved by randomly screening a selected sample of women with ultrasound, to provide cumulative incidence estimates for black and white women. The difference between the age-specific cumulative incidence curves for black and white women was still highly significant (odds ratio, 2.9; 95% CI, 2.5-3.4; $P < .001$) (figure 1), but less than that suggested by Nurse' Health Study. Interestingly, the estimated cumulative incidence of fibroids by age 50 was a >80% for black women and nearly 70% for white women (figure 2).

Both these recent studies, however, have focused on American women. There is evidence that different populations have different prevalence rates. A study in Sweden of 334 women revealed that for women who were 33 to 40 years old, the prevalence was only 8% compared to the NIEHS study of 26% for white women and 53% of black women, of the same age ⁷. Why there should be these population differences is not clear, but some of the researched aetiological variables are described below.

One variable that has been the focus of considerable research and debate is the association between oral contraceptive use and the risk of developing uterine fibroids. Amongst ever users, the risk of hysterectomy-confirmed leiomyomata has been observed to be reduced ^{8;9}, not associated ¹⁰ or elevated ¹¹.

The more recent Nurse' Health Study II reported on a number of variables in relation to leiomyomata development, including contraception use ¹². This large prospective study reported that fibroids were inversely associated with early menarche, parity and positively associated with a history of infertility. With regard to contraceptive use, amongst ever users the risk of fibroid development was similar to that amongst never users (relative risks 1.03; 95% CI 0.93-1.15). In contrast, current users compared to never users appeared to be at a slightly reduced risk of developing fibroids (RR 0.80; 95% CI 0.67-0.94). Of interest in this study was the finding that early use of oral contraceptive at ages 13-16 was strongly associated with a hysterectomy confirmed diagnosis (RR 1.90; 95% CI 1.29-2.79) compared to never users. Another recent study, this time a case-control one, reported on the same risk factors in 2000 women. The authors reported similar results to the Nurse' Health Study II ¹³.

Other factors that have been studied include body mass index and smoking. Whilst the former appears associated with a modest increased risk of uterine fibroids ¹⁴, the association with smoking appears less clear^{14;15}.

Finally researchers have studied the effect of diet and its association with uterine fibroids ¹⁶. Neither coffee, tea nor alcohol appeared associated with fibroids. Red meat was positively associated with fibroids (OR 1.7; 95% CI 1.4-2.2), whereas a high intake of green vegetables and fish appeared to have a protective effect (OR 0.5; 95% CI 0.4-0.6 and OR 0.7; 95% CI 0.6-0.9).

Pathology

Gross Features

Leiomyomas are generally white, spherical, firm lesions that are well circumscribed. When cut, they tend to bulge over the adjacent myometrium and the criss-cross of the smooth muscle bundles creates a classic “whorled” or “trabeculated” appearance.

They are classified according to their location within the uterus and are described as being either, submucosal, intramural (the commonest site) or subserosal. In two thirds of cases they are multiple ⁴.

Occasionally, larger leiomyomas undergo degeneration. This gives rise to dark red areas, as a result of haemorrhage or to soft and yellow areas, as a result of necrosis. Fibroids that have previously undergone infarction or degeneration can also develop white or translucent fibrous scars, focal cystic areas, mucinous areas and sometimes calcification.

Microscopic

On microscopic examination the smooth muscle cells of leiomyomata appear elongated (spindled) and bundled together (fascicles), criss-crossing each other at right angles. These fascicles can extend long distances and account for the “whorled” gross appearances. The nuclei are centrally located and often described as being “cigar like” because of their elongated shape and blunt ends. They have abundant amounts of eosinophilic cytoplasm, which stains for antibodies against muscle-specific actin, alpha smooth muscle actin, and desmin on immunohistochemistry. There is typically no cellular atypia, increase in mitotic activity or tumour necrosis.

Surrounding and supporting the smooth muscle fascicles are variable amounts of fibrous tissue and collagen.

Foci of degeneration and infarction are common in leiomyomas and microscopically appear as oedema, haemorrhage, hyaline necrosis and fibrosis. Hyaline necrosis occurs secondary to ischaemia and can be identified in over half of all leiomyomas. It is characterized by the replacement of smooth muscle cells by eosinophilic fibrillary material that frequently surrounds necrotic smooth muscle cells. Haemorrhagic areas are frequently focal and sharply demarcated.

Several microscopic variants of leiomyomas have been described and a brief description of the more common ones will follow (They are summarised in Table 1). For a more complete description the reader is referred to two excellent review articles ^{2 17}.

- Cellular leiomyomas

These are leiomyomas that appear significantly more cellular than normal myometrium. The tumours almost always have <5 mitotic figures per 10 high-powered field. There is no cellular atypia or necrosis.

- Leiomyomas with bizarre nuclei

These leiomyomas, also known as atypical leiomyomas have focal areas of highly bizarre cells, with enlarged cytoplasm and nuclei (giant cells).

- Mitotically active leiomyomas

These are otherwise typical leiomyomas or cellular leiomyomas that have an increased number of mitotic figures, usually between 5 and 15 per high power field.

- Smooth muscle tumours of uncertain malignant potential

Indicators of malignancy in leiomyomas are increased cellularity, nuclear atypia and increased mitotic activity with atypical mitotic figures. Smooth muscle tumours of uncertain malignant potential do not exhibit all these features, but instead typically demonstrate two of varying severity.

- Leiomyosarcomas

This section would not be complete without mentioning leiomyosarcomas.

These malignant tumours tend to arise de-novo from smooth muscle cells and women with pre-existing multiple leiomyomas do not seem to be at additional risk. They are typically solitary and poorly circumscribed. On microscopic examination, they are hypercellular, exhibit cellular pleomorphism, excess mitotic activity and necrosis. They are aggressive cancers with a recurrence rate of 71% in one series ¹⁸, and a median survival time of 10 months in another ¹⁹.

Pathogenesis

The underlying pathogenesis and pathophysiology of leiomyomas is highly complex and is far from being completely understood. However, in recent years with the mapping of the human genome and advances in molecular biology the interplay between genes, ovarian steroids and growth factors that result in fibroid development, is slowly being elucidated.

Genetic factors

Cytogenetic examination of leiomyomas, reveals that about 40% of them have chromosomal abnormalities²⁰. These consist of translocations, trisomies, deletions and rearrangements²¹. The rest appear chromosomally normal but may exhibit mosaicism within the monoclonal tumour. These karyotype abnormalities have been shown to correlate with fibroid size and site, with deletions on chromosome 7 resulting in smaller tumours compared to rearrangements on chromosome 12 (5.0 vs 8.5 cm)²². The mechanisms that link these clinical phenotypes to their underlying genotypes varies. For example, translocations can either up-regulate or down regulate a gene and its expressed protein, depending on where the gene sequence is spliced. Trisomies on the other hand generally increase gene expression, through increased gene dosing.

Of those fibroids that exhibit cytogenetic abnormalities detected on light microscopy, by far the commonest mutation to date are translocations. The commonest of which is t(12;14) (q14–15;q23–q24), which occur in approximately 20% of fibroids with karyotypic rearrangements²³. Other less

common translocation partners of chromosome 12 include chromosomes 2, 4, 22, and X ²⁴.

Abnormalities in the region q14-15 on chromosome 12 have also been reported in other benign mesenchymal neoplasms, such as lipomas and salivary gland adenomas ^{25 26}, suggesting the presence of a gene or genes important in tumorigenesis. Indeed, subsequent research has revealed the presence of the gene HMGIC within this region. This critical gene codes for the high mobility group (HMG) protein of the same name. There are a number of HMG proteins, but they all act to indirectly regulate DNA activities, such as transcription, by serving as architectural factors. Soon after the mapping of the HMGIC gene, another HMG gene, HMGIY was discovered on the short arm of chromosome 6 and again discovered to be expressed in fibroids. However, HMGIY differs from HMGIC in that it is also expressed in chromosomally normal fibroids.

How HMG proteins act and how they might be involved in tumorigenesis is complicated, but by binding to the DNA they reconfigure its structure, thereby affecting the actions of other DNA binding proteins. For example they have been shown to affect the transcription of a number of cytokines and growth factors such as interleukin 2 (IL-2) and nitric oxide synthase ^{27 28}.

Before moving on to the role of endocrine and growth factors in fibroid development it is worth mentioning research looking at the familial inheritance of fibroids. Very briefly, twin studies have shown a strong susceptibility to

fibroid development, with monozygotic twins twice as likely to develop fibroids compared to dizygotic twins ²⁹. Familial clustering is well described ³⁰ and there are also several inherited disorders associated with fibroids such as Reed syndrome ³¹, Cowden disease and Bannayan-Zonana syndrome. These studies are important because they provide insights into the location of the genes involved in the pathogenesis of leiomyomas.

Ovarian steroids and growth factors

The ovarian steroids oestrogen and progesterone are important in the pathogenesis of fibroids ³². It has been shown that leiomyomas have increased levels of oestrogen and progesterone receptors when compared to normal myometrium ³³, and that they also have increased expression of the enzyme P450 that allows the cells to synthesize their own endogenous oestradiol ³⁴. Oestrogens affect tumour growth by stimulating the proliferation of uterine smooth muscle cells ³⁴. Progesterone on the other hand, through its production of the bcl-2 protein, increases tumour bulk, by inhibiting programmed cell death ³⁵.

Growth factors increase smooth muscle cell proliferation and act in a paracrine or autocrine way. They are also responsible for the increase in the extracellular matrix associated with so many leiomyomas. This matrix consists of collagens, proteoglycans and fibronectin. The growth factors identified to date include transforming growth factor β (TGF β), heparin-binding factors and insulin-like growth factors.

Transforming growth factor β (TGF β), increases the production of fibronectin and collagens ³⁶ and decreases collagenase production. It is abnormally expressed by leiomyomas. The heparin-binding growth factors include the fibroblast growth factors (FGF), heparin-binding epidermal growth factor, vascular endothelial growth factor and platelet derived growth factor. These increase cell proliferation and also stimulate blood vessel formation (angiogenesis) ³⁷. Finally, the insulin-like growth factors (IGF) are small polypeptides that promote cell proliferation and differentiation. IGF-I has been found to be abnormally expressed in leiomyomas compared to normal myometrium ³⁸. It appears to be even more potent in combination with epidermal growth factor or platelet derived growth factor ³⁹.

Clinical Features

Fibroids are associated with heavy and prolonged periods, reproductive dysfunction and pain. In addition their site and or size can affect the bladder and bowel, resulting in frequency of micturition, constipation and in extreme cases renal failure from ureteric obstruction ^{3,40}.

There are several mechanisms that might explain their association with abnormal bleeding. Firstly, fibroids tend to increase the endometrial surface, therefore increasing the volume of endometrium shed each month. Secondly, they are associated with angiogenesis and abnormal vessel characteristics ⁴¹. Finally it is possible that they interfere with normal uterine contractility at the time of menstruation.

The association with reproductive dysfunction has long been reported ³. However, good evidence supporting this has been scarce. Studies in the past have been retrospective, of insufficient size to confirm or detect any differences and have not distinguished between submucous, intramural or subserous fibroids. Fortunately, as a result of studies from reproductive medicine units this is changing. Such studies have already shown that submucous fibroids adversely affects fertility outcome ⁴² and more recently it has been shown that intramural fibroids reduce the chance of an ongoing pregnancy by a factor of 0.46 (0.24-0.88, $p=0.02$) ⁴³. Suggested mechanisms that explain these findings include distortion of the uterine cavity, reduced implantation (the endometrium overlying submucous fibroids is often atrophic), and impairment of the rhythmic uterine contractions that facilitate the passage of sperm through the uterus.

Fibroids cause acute pain, either by undergoing torsion (if pedunculated) or by undergoing degeneration. In case of the latter, the fibroid outgrows its blood supply resulting in tissue ischaemia and necrosis. Red degeneration typically occurs in pregnancy. Here, bleeding occurs within the fibroid, causing acute pain. Fibroids are also associated with dyspareunia and noncyclic pelvic pain ⁴⁴. However, they do not appear to be associated with dysmenorrhoea.

It is easy to see how an enlarged fibroid uterus can compresses the bladder anteriorly or the rectum/sigmoid posteriorly to give rise to bladder and bowel symptoms. Renal compromise is rare but is more likely when the leiomyomas are present in the broad ligament, close to the ureters.

Medical and Non-surgical Treatments

Medical

Current medical therapies for fibroids are limited. They include the combined oral contraceptive pill, non-steroidal anti-inflammatory drugs (NSAIDs), and various regimes based on gonadotrophin releasing hormone analogues (GnRHa). As with all treatment options for fibroids, data on their efficacy is limited or absent ⁴⁵.

Low dose oral contraceptives have been reported to reduce menstrual flow and increase the haematocrit without increasing uterine size ⁴⁶. Naproxen, a NSAID, has also been evaluated as a treatment for menorrhagia. Whilst it appeared successful in reducing blood loss in women with dysfunctional uterine bleeding, it did not appear effective in reducing blood loss in women who had fibroids ⁴⁷. GnRHa have been more rigorously assessed than the above agents and they are effective when used preoperatively to reduce tumour size and correct anaemia⁴⁸. Some researchers have evaluated GnRHa in their own right, rather than as adjuncts to a surgical approach. The limiting factor is oestrogen deficient side effects and a regrowth of leiomyomas upon cessation of the standard six-month treatment course (any longer results in osteopenia and increases the risk of fractures). To overcome these problems, various hormone replacement treatments have been “added back”^{49;50}. As a result, some have suggested it might even be possible to control fibroid related symptoms until the menopause with intermittent GnRHa courses ⁵¹.

Other reported medical agents currently being evaluated or in development include the anti-progesterone mifepristone, the anti-fibrotic drug perfenidone, the alkylid halofuginone, and interferone therapy ^{37;52}.

Non-surgical treatments

There are two non-surgical treatment alternatives that are at different stages of development. The first is uterine artery embolisation (UAE). This is a radiological procedure that uses angiography to visualise the uterine arteries. The approach is usually unilateral, via the femoral artery and aims to block (embolise) the lumen of the uterine arteries by injecting them with micro-particles, typically in the form of polyvinyl alcohol. It was first described as a pre-operative technique to reduce intraoperative bleeding at myomectomy ⁵³ before being reported in it's own right as a treatment option ⁵⁴. The ischaemia it induces essentially infarcts the fibroids, resulting in hyaline degeneration, a reduction in tumour size and relief of associated symptoms. However, experience of the technique remains limited. To date, the largest published observational series has only involved 400 women ⁵⁵. The authors in this study reported a subjective improvement in menstrual bleeding of 84% at a mean follow up of 16.7 months and a 53% reduction in uterine volume based on magnetic resonance imaging (MRI). The reported rate of hysterectomy was 3%.

UAE is not without significant morbidity. Of the three reported deaths in the literature two occurred from fatal septicaemia ^{56;57} and the third from pulmonary embolism ⁵⁸. One of the main concerns surrounding the procedure

is non-target embolisation. This can result in severe buttock pain from inadvertent embolisation of the superior gluteal artery ⁵⁹ or in transient ovarian failure via utero-ovarian anastomosis ⁶⁰. Some report the latter is far from transient with an overall figure of ovarian failure in 15%, rising to 43% in embolized women older than 45 years ⁶¹. Indeed, the same researchers, based on prospective sonographic assessment of the ovarian arterial circulation, suggest that inadvertent embolization of the ovarian arterial bed occurs routinely during UAE ⁶².

As a result of the controversy surrounding the procedure, the Australian Gynaecological Endoscopy Society have recently called for a moratorium on UAE until more evidence is available ⁶³. In the UK, a working party set up by the Royal College of Obstetricians and Gynaecologists examined UAE and reported in 2000. The group comprised of both interventional radiologists and gynaecologists. They made a number of recommendations, including establishing a national database and only offering UAE to infertile women within the context of a clinically controlled trial, because of concerns about adverse effects on fertility ⁶⁴.

The other non-surgical technique that is currently being evaluated for the treatment of symptomatic fibroids is percutaneous MRI guided laser ablation. This technique evolved from laparoscopic laser ablation of fibroids ⁶⁵ and was first reported in 1999 ⁶⁶. Under real time MRI, 18 gauge needles are inserted percutaneously into the largest fibroid under local anaesthetic. Neodymium: yttrium-aluminium-garnet (Nd YAG) laser fibres are then passed through the

lumen of the needles and thermal energy delivered. The temperature changes are thermally mapped in real time. A temperature of 55°C has been deemed to cause irreversible tissue damage.

To date there is an ongoing observational pilot study. Provisional data on 66 women showed a mean reduction in fibroid volume of 31% ($P < 0.001$) and an objective reduction in menstrual blood loss ⁶⁷. However the data set for the menstrual blood loss outcome consisted of only 8 women.

Table 1: Distinguishing features of leiomyoma and leiomyosarcoma

Atypia	Mitotic Activity	Cellularity	Diagnosis
Absent	0-4	Normocellular	Benign leiomyoma
Absent	5-15	Normocellular	Mitotically active leiomyoma
Absent	0-4	Hypercellular	Cellular leiomyoma
Minimal	(\geq)5	Hypercellular	Uncertain malignant potential
Present	0-4	Variable	Atypical leiomyoma
Present	(\geq) 5		Hypercellular leiomyosarcoma

Source: Zaloudek C ¹⁵⁰

figure 1. The proportion with newly detected leiomyoma among Women with no previous diagnosis of leiomyoma, by age group. The *closed bar* denotes black women; the *gray bar* denotes white women ⁶

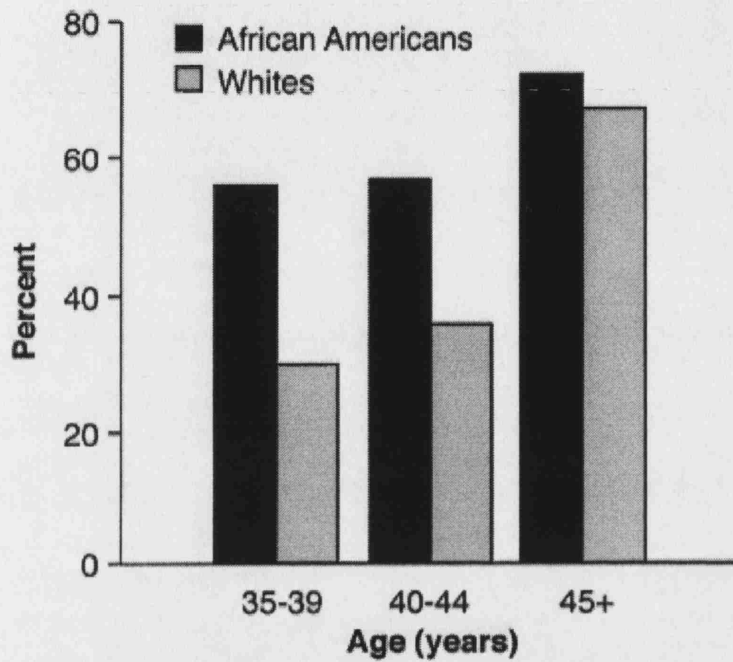
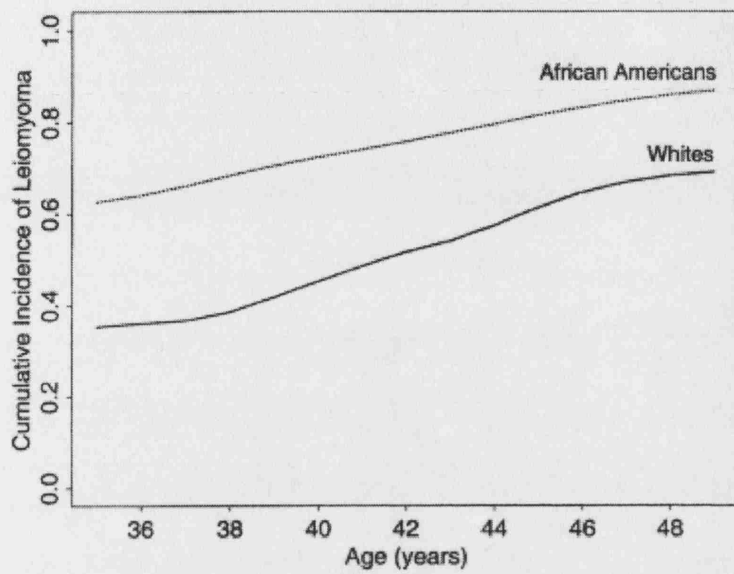


figure 2. Estimated age-specific cumulative incidence of uterine leiomyoma for black women and white women, aged 35 to 49 years ⁶.



Chapter Two: Background to thesis

Historically, symptomatic fibroids have been managed surgically and traditionally via laparotomy ⁶⁸, although there are reports of some being removed vaginally ⁶⁹. More recently they have been managed hysteroscopically ⁷⁰ and laparoscopically ⁷¹. The route chosen depends on site, size of fibroid ⁷², local resources and patient choice. However, it is not currently clear how prevalent these approaches are. Therefore, one of the aims of my research was to determine the current surgical techniques used when managing symptomatic fibroids.

Whilst the aim of surgery is to affect a cure or at worst relieve symptoms, by its invasive nature, it is not without morbidity and each route has its advantages and disadvantages. The main challenge that the surgeon faces is the control of intra-operative bleeding, which can be massive. Indeed the main focus of my research was evaluating modified triple tourniquets both at laparotomy and laparoscopically as a technique to improve haemostasis.

Open myomectomy remains the most likely treatment option and surgical route in the UK, with 1,414 open myomectomies being performed in 2001, accounting for 7,597 bed days ⁷³. Recent data for the USA show that 37,000 myomectomies are performed annually ⁴⁵. However, it is a major surgical procedure with potentially considerable operative morbidity. One recent study, for instance reported that 23% patients lost over 1000 mls of blood ⁷⁴. Other series reported transfusion rates between 18% and 24% ^{75 76 77}.

In an effort to reduce the morbidity associated with this blood loss a number of techniques have been described. These include pre-operative medical

therapy with gonadotrophin releasing analogues (GnRHA) ⁴⁸ and intra-operative mechanical tourniquets ^{68;78} or chemical tourniquets ^{74;76}. However, none of these are ideal and in particular the above techniques are designed primarily to reduce intra-operative blood loss, rather than post-operative bleeding from the uterine incision(s), which remains a potential problem ⁷⁹⁻⁸¹.

We therefore sought to improve on the triple tourniquet concept by using an absorbable polyglactin suture tied around the cervix (to act as the uterine artery tourniquet, leaving it in situ at the end of the operation) in an attempt to reduce both intra- and post-operative bleeding at open myomectomy.

Although the use of tourniquets is well established, data from randomised controlled trials is scarce and more importantly, their effect on ovarian function has not been researched. Theoretically, laterally placed ovarian vessel tourniquets used to occlude the blood supply to the uterus from above could in principle effect ovarian function. Therefore, for the first time we sought to evaluate triple tourniquets, our novel modification and to determine their effect on ovarian function within the context of a randomised controlled trial.

Finally, although the removal of fibroids might seem the logical cure for associated symptoms good data on the efficacy of this operation is lacking ⁴⁵. We therefore sought, again for the first time, to obtain prospective data on the effect of open myomectomy on menorrhagia and quality of life.

Laparoscopic myomectomy is a “keyhole operation” that has been developed as an alternative to open myomectomy ^{71;72;82;83}, the rationale being that the

smaller the surgical incision, the less of an insult to the abdominal wall and therefore the quicker the patient will recover and mobilise following surgery. Evidence from randomised trials, appears to support this ^{84;85}.

In addition to laparoscopic myomectomy, a number of other endoscopic techniques have been described, including laparoscopic myolysis (in situ destruction of the fibroid either with diathermy or laser) ^{82;86}, myolysis achieved by occluding the uterine arteries with bipolar electrosurgery ⁸⁷, and hand-assisted laparoscopy for megamyomectomy ⁸⁸. For my thesis, I shall only be considering the technique of laparoscopic myomectomy (the removal of fibroids, usually by morcellating, through keyhole incisions in the abdominal wall) ⁷¹.

As at open surgery, intraoperative bleeding can be significant during the laparoscopic approach. When the technique was first described, the chemical tourniquet vasopressin was used, and though vasoconstrictor agents are effective ⁷⁴, they are not without morbidity and inadvertent systemic injection can result in cardiovascular and pulmonary complications ⁸⁹. As a result, these drugs have been banned in some European countries, notably France.

As an alternative to the use of vasoconstrictors, some surgeons have ligated the uterine arteries, either permanently with vascular clips or temporarily with a number 0-Polydioxanone (PDS) Endoknot ⁹⁰, prior to excising the fibroids from the uterus. However, even these alternatives have their drawbacks. The final arm of the research was therefore to see if the new triple tourniquets that

we had developed to reduce the morbidity at open surgery could be used to potentially reduce the morbidity at laparoscopic myomectomy.

Chapter Three: Consultant survey

Introduction

Uterine fibroids are the commonest benign tumour in women with a accumulative incidence of >80% for black women and 70% for white women at 50 years of age ⁶. Despite the introduction of new surgical and non-surgical techniques ^{54;90-92}, myomectomy remains the mainstay of treatment for symptomatic fibroids. In the UK in 2001, 1,414 open myomectomies were performed, accounting for 7,597 bed days. Specific data for endoscopic myomectomy is not available but in 2001 there were, 18,880 therapeutic endoscopic operations on the uterus ⁷³. In the same period 393 UAE were performed accounting for 1451 bed days.

Endoscopic removal of fibroids shortens the length of hospital stay and hastens the return to full activity ^{84;85}. However not all United Kingdom (UK) Consultant Obstetricians & Gynaecologists offer operative endoscopy. In addition there are variations in practise amongst those that do. This survey, for the first time reports on the route of surgery, the haemostatic techniques employed at myomectomy and the availability and use of uterine artery embolisation.

Patients and Methods

The correspondence addresses of all UK Consultant Obstetricians & Gynaecologists were obtained with approval from the Royal College of Obstetricians & Gynaecologists. In addition Local Ethics Committee approval was obtained (Application No. 5855). The questionnaire was a double sided, pink coloured page, A4 size and comprised of 27 questions. Generated on

Pinpoint® software, it consisted initially of general questions about place of work, year of qualification before going on to ask in detail about open myomectomy, laparoscopic myomectomy, hysteroscopic myomectomy and uterine artery embolisation. Finally, respondents were asked to rank symptoms, in order that they were best treated by myomectomy. We did not ask if the survey was completed from memory or whether case notes or databases were reviewed.

The questionnaire was initially piloted in-house, before being posted out to each Consultant. Non-responders were sent one reminder questionnaire. The data was then analysed using Pinpoint ® 2(Cambridge Software Publishing, Cambridge, United Kingdom) and SPSS® 11 software (SPSS Software, Chicago, Illinois, USA).

A copy of the questionnaire is provided in Appendix 1.

Statistics

The returned forms were entered into Pinpoint ®. The data was then analysed and outputted within Pinpoint ®. Where further analysis was required, the data was imported into Microsoft ® Excel 2002 and then outputted using Graph Pad Prism ® 4 software (GraphPad Software, San Diego California, USA).

Results

Of the 1439 Consultants surveyed, 852 replied giving a response rate of 59%.

General Information

Seven hundred and thirty five Consultants (86%) performed regular sessions of gynaecology surgery. The median age of qualification was 1979 (range 1955-1992) and the average year of membership of the Royal College of Obstetricians and Gynaecologists was 1986 (range 1964-2001). Five hundred and thirty six respondents (63%) worked in a District General Hospital, two hundred and twenty seven (27%) worked in a Teaching Hospital and twenty-four (3%) worked solely in the Private Sector. The remaining seven percent did not specify their place of work.

Imaging

Seven hundred and eighty four respondents replied to the question about imaging of the fibroid uterus. Of these 82% used ultrasound to assess the site and size of fibroids, 13% MRI, 3% CT and the remainder used no imaging modality.

Open myomectomy

Five hundred and fifty (64%) Consultants performed at least one open myomectomy in 2001, with the majority (51%) performing between one and five procedures a year (Figure 7). When asked what was the smallest uterus they would manage by open myomectomy, two hundred and twenty-four (41%) replied a uterus equivalent to 12 weeks gestational size or less. Ninety-nine respondents (18%) would perform a third open myomectomy, and one hundred and fifty-five (28%) would perform an open myomectomy on a woman over 50 years of age.

Four hundred and ninety-five gynaecologists (90%) admitted to regularly using a specific technique to reduce operative bleeding (figure 8). Four hundred and sixty-six (85%) prescribed pre-operative gonadotrophin releasing hormone agonists (GnRHa), whereas intraoperative techniques were more varied and often used in combination (e.g. vasoconstrictors and cutting diathermy). Other techniques to reduce operative bleeding included supraselective embolisation (5%). One hundred and seventy (31%) reported the need for regular blood transfusions with rates varying from less than ten percent (20%) to more than thirty percent (3%).

Laparoscopic myomectomy

Ninety (11%) Consultants performed laparoscopic myomectomy in 2001 (Figure 9). The average uterine size managed laparoscopically was equivalent to a 12 weeks gestation (range 8 to 20 weeks). Nineteen (21%) would perform a laparoscopic myomectomy on a woman over 50 years of age. Thirty-five (39%) regularly used specific haemostatic techniques, cutting diathermy and pre-operative GnRHa being the commonest; only one (1%) Consultant used tourniquets (Figure 10). Of the eighteen who reported the need to convert to laparotomy, the median rate reported was 5% (range 1-5% to >20%). Of the twelve respondents who reported the need for transfusion post-operatively, nine (10%) transfused up to 10% of patients; the remaining three reported a transfusion rate of 20%.

Hysteroscopic myomectomy

Three hundred and sixty-four (43%) respondents performed hysteroscopic myomectomies. Of these, the majority (57%) carried out ≤ 5 cases a year, while thirty-one (9%) operated on > 20 cases in 2001 (Figure 11). The median size of uterus managed by hysteroscopic myomectomy was equivalent to 12 weeks gestation (range 8 to 20 weeks). Twenty-four (7%) Consultants reported the need for a blood transfusion in up to ten per cent of cases. Ten (3%) reported the need to convert to laparotomy, with a median rate of conversion of 5% (range 1-5% to $>20\%$).

Uterine artery embolisation

Four hundred and thirty-nine (51%) respondents replied they had access to UAE. Of this group, the median number of patients referred annually was five (range 0 to >20) (figure 12). One hundred and fifty-five Consultants (26%) replied they would recommend UAE to a patient wanting to conceive.

Symptoms best treated by myomectomy

Abdominal mass was ranked as the commonest indication for myomectomy, followed by menorrhagia and pelvic pressure (2nd equal), urinary symptoms (4th) and infertility (5th).

Discussion

This survey reports on the current surgical and radiological management of symptomatic fibroids in the UK. The questionnaires may have been completed from memory and therefore recall bias cannot be excluded in interpreting the results. For instance this might have caused respondents to overestimate the total number of procedures or to underestimate the number of complications. However, until more robust and user-friendly hospital databases are the norm rather than the exception, such retrospective surveys will struggle to avoid this kind of bias. Nevertheless I still believe the results are of interest to the gynaecological community.

Of the 75% of Consultants performing open myomectomy, 87% used GnRHa pre-operatively. GnRHa is effective in reducing blood loss but can make the surgery more difficult by causing fibrosis between the tissue planes⁹³. In addition, such pre-treatment has been shown to be associated with an increase in fibroid recurrence at six months⁹³. Intra-operative techniques to reduce blood loss varied, with the use of cutting diathermy on the uterus and myomectomy clamps⁶⁸ being the most popular. Significant numbers used vasoconstrictors and tourniquets.

The reported transfusion rate of up to 10% for 20% at open myomectomy is less than that reported in the literature^{74;94}. This result may be genuine but could reflect recall bias of a complication. With regard to imaging of the fibroid uterus, ultrasound is the most frequently used technique, doubtless reflecting

its widespread accessibility, even though magnetic resonance imaging is probably superior ^{95;96}.

Laparoscopic myomectomy was first described in 1979 ⁷¹, the average year of medical school graduation for responders. However more than twenty years on, only 11% of our sample are performing laparoscopic myomectomy. In contrast, 41% are performing open surgery on a uterus equivalent to 12 weeks gestation, a size that can usually be managed laparoscopically ⁸³. The reasons why laparoscopic surgery for fibroids has failed to become popular was not the focus of our survey, but is likely to reflect a lack of training, the non-availability of instruments such as morcellators, and not least, concerns about prolonged operating times.

As at laparotomy, GnRHa are preferred pre-operatively and intra-operatively cutting diathermy and vasoconstrictor agents were the most favoured techniques to reduce blood loss at laparoscopic myomectomy. The fact that a number of techniques are used probably reflects the fact that, while one haemostatic technique is better than nothing, none is ideal. For instance GnRHa are a risk factor for conversion to laparotomy ⁹⁷ and vasoconstrictor agents can be associated with severe iatrogenic injury ⁸⁹.

The finding that 21% of respondents would perform a laparoscopic myomectomy and 28% an open myomectomy on a woman over 50 years of age, where historically they might have performed a hysterectomy is

interesting. This may well reflect an increasing demand for uterine preserving surgery and a societal trend away from hysterectomy.

The survey clearly shows that UK Consultants are more likely to have removed fibroids hysteroscopically than laparoscopically, although even this route was utilised relatively infrequently by the majority. Whilst the median size of uterus managed hysteroscopically was 12 weeks, a minority would operate on uteri up to 20 weeks despite the greater potential for fluid overload

98

Uterine artery embolisation was first developed as a pre-operative technique to reduce intra-operative blood loss. However, it was noted that embolisation was associated with significant shrinkage of the fibroids and an improvement in symptoms that obviated the need for surgery. More than half the responders in this survey reported having access to interventional radiologists offering this procedure. Interestingly, 26% recommended UAE to a woman wanting to conceive despite the current Royal College of Obstetricians & Gynaecologists guidelines recommend that it should be only offered in these circumstances in the context of a controlled clinical trial ⁶⁴.

figure 7 Number of open myomectomies performed in 2001

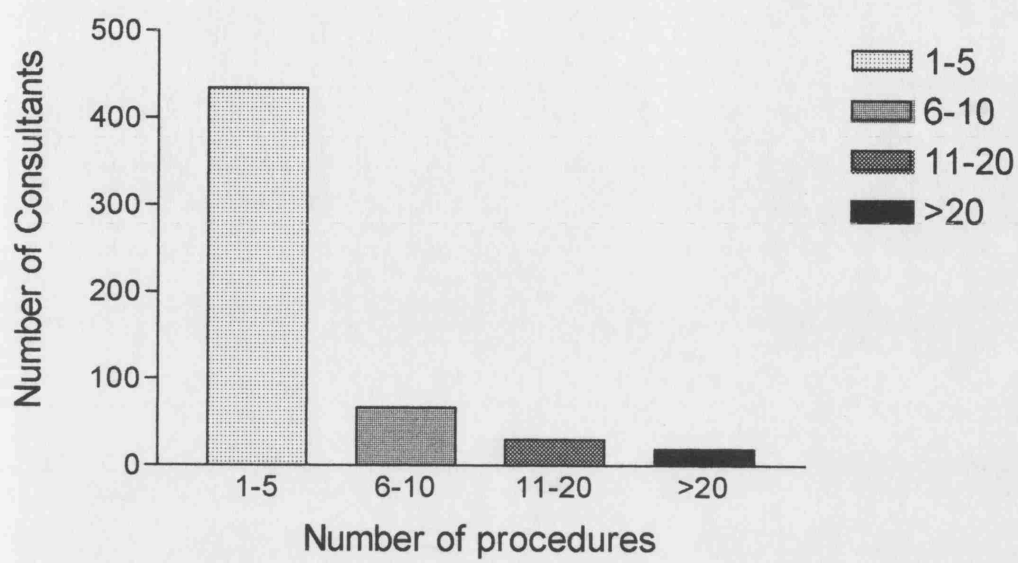


figure 8 Haemostatic techniques used at open myomectomy (several used more than one)

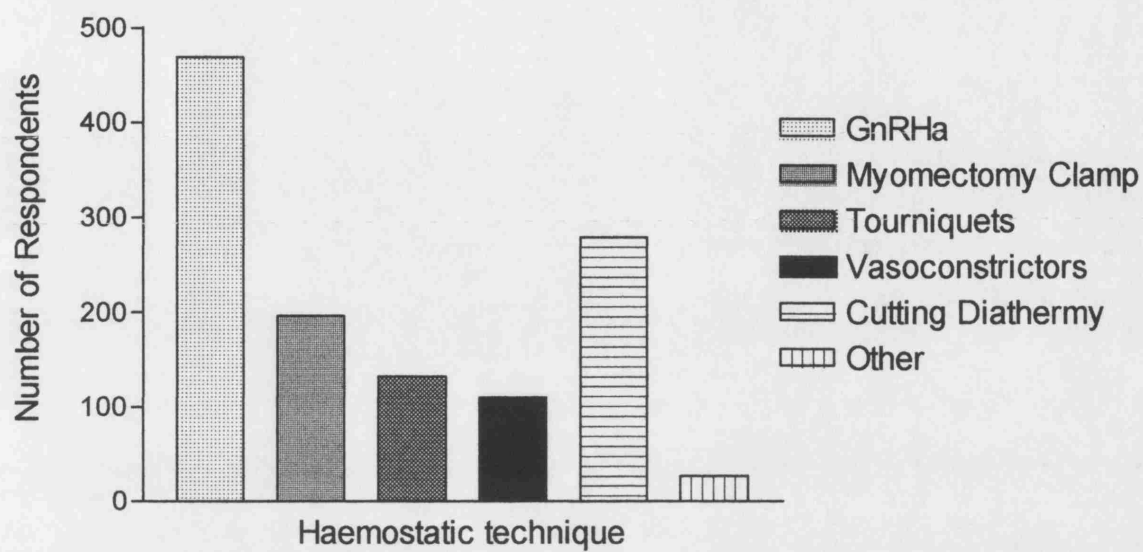


figure 9 Number of laparoscopic myomectomies performed in 2001

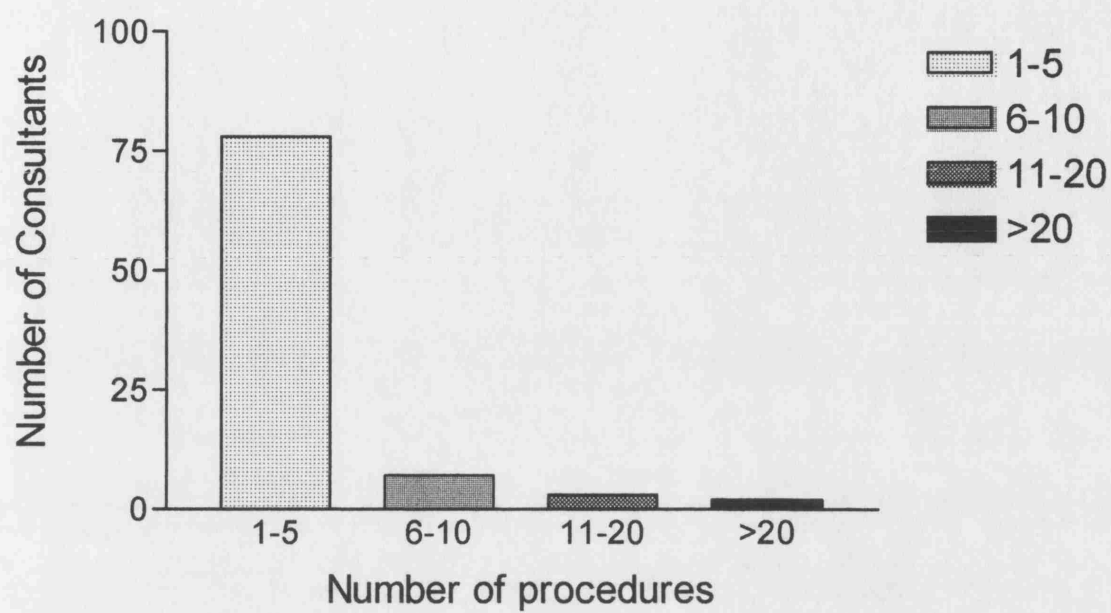


figure 10 Haemostatic technique at laparoscopic myomectomy

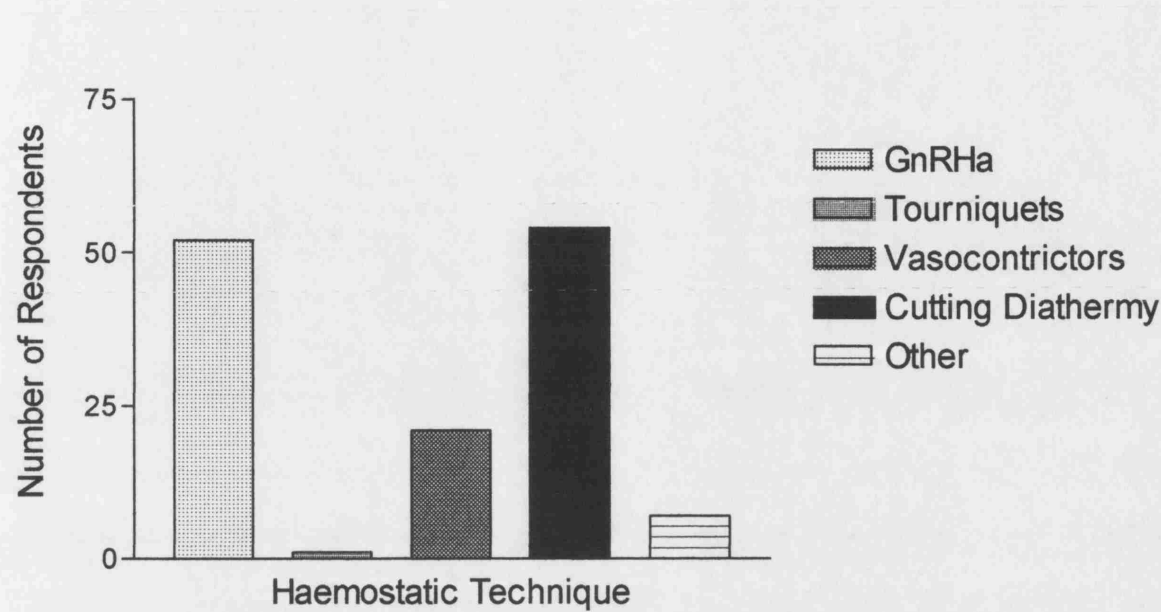


figure 11 Number of hysteroscopic myomectomies performed in 2001

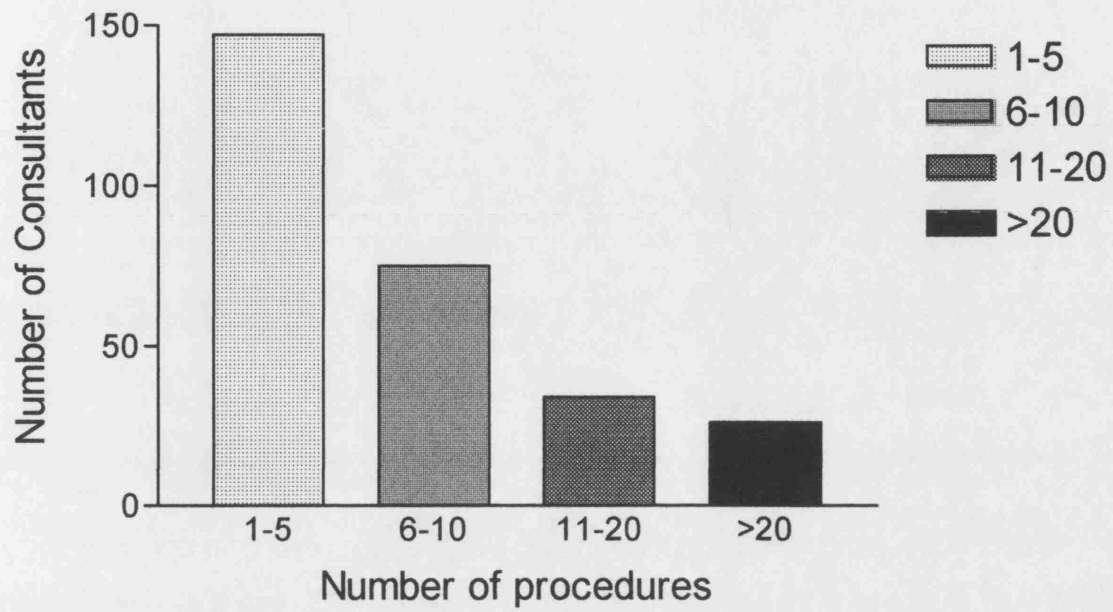
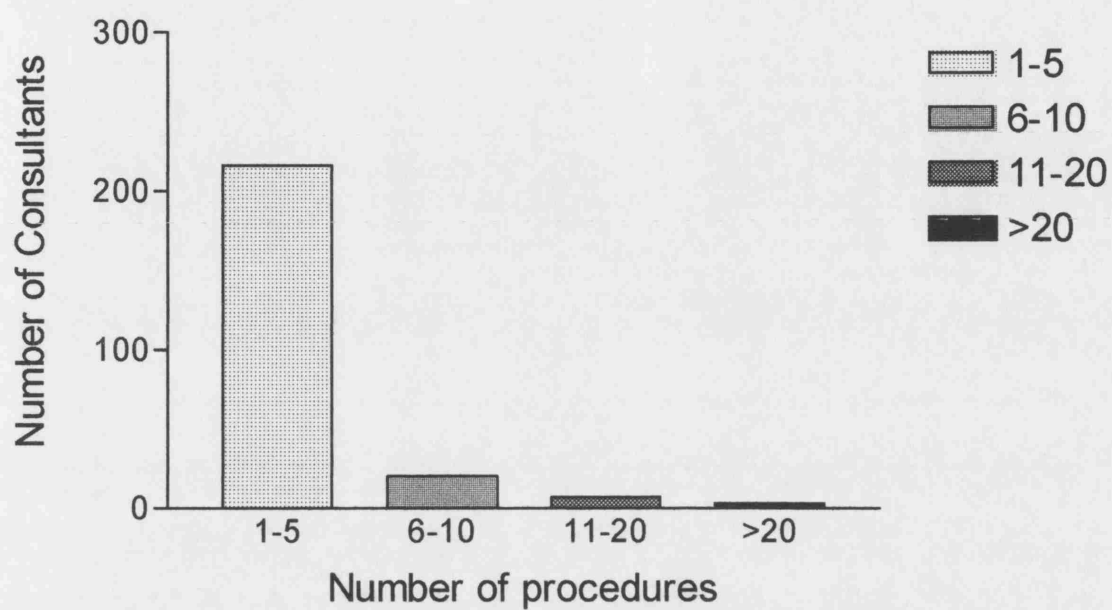


figure 12 Number women referred by Consultants for Uterine Artery Embolisation in 2001



Chapter Four: Prospective randomised controlled trial of triple tourniquets at open myomectomy

Introduction

Improvements in diagnostic imaging reveal that uterine fibroids are more prevalent than originally described³, recent data suggesting a cumulative incidence of at least 70% for a woman aged 50 years of age⁶. When symptomatic, fibroids are associated with reproductive dysfunction, abnormal bleeding and pelvic pressure symptoms. Recent evidence has also suggested a link with dyspareunia and noncyclic pelvic pain⁴⁴.

In the UK in 2001 1,414 open myomectomies were performed⁷³. By comparison 44,461 hysterectomies were performed in the same period. Recent data for the USA show that 37,000 myomectomies are performed annually⁴⁵. Open myomectomy is a major surgical procedure and is associated with considerable morbidity, in particular operative. One recent study, for instance, reported that 23% patients lost over 1000 mls of blood⁷⁴. Other series reported transfusion rates between 18% and 24%^{75 76 77}.

Haemostatic tourniquets to reduce intra-operative bleeding have long been available⁹⁹, but data on their efficacy from controlled trials is lacking. We set out to evaluate the use of triple tourniquets in controlled conditions and for the first time investigate the hypothesis that leaving a semi-permanent tourniquet around the uterine artery reduces postoperative bleeding from the uterine incisions, a well recognised sequel to surgery⁷⁹⁻⁸¹.

Patients and Methods

Study Participants

From January 2002 to July 2003, patients seen in the Fibroid Clinic and Gynaecology Clinic at the Royal Free Hospital, and Gynaecology Clinic at the Whittington Hospital, London, were assessed for entry into this randomised controlled trial. Entry criteria were symptomatic fibroids, a uterine size equivalent ≥ 14 weeks gestation and a request of myomectomy. Exclusion criteria were a history of a bleeding disorder, concurrent anticoagulant therapy, a haemoglobin less than 10.5 g/dl at the time of surgery, and premalignant endometrial histology.

Diagnosis of uterine fibroids was based on clinical examination and ultrasound scan. Women complaining of abnormal uterine bleeding (e.g. menorrhagia, intermenstrual bleeding) underwent outpatient diagnostic hysteroscopy and endometrial biopsy.

Pre-operative gonadotropin releasing hormone agonists (GnRHa) were only prescribed if the patient was anaemic (Hb < 10.5 g/dl) or if uterine size was > 20 weeks gestation size (to facilitate the use of a low transverse incision at myomectomy).

The study protocol was approved by the Local Ethics Committee (Application No. 5855).

Power Calculation

Based on a review of the published literature^{74;102}, we hypothesised that 75% of our control group would lose more than 500 mls of blood compared with 25% of those managed with tourniquet. For the probability of a type 1 statistical error (two-sided) to be less than 0.05 and the probability of a type 2 error to be less than 0.2 we calculated that we would need 14 patients in each group, giving a total of study size of 28 women.

Randomisation

Patients were allocated to the control or tourniquet by means of sealed, sequentially numbered opaque envelopes containing computer-generated random numbers. Randomisation was done immediately before surgery, and patients were not informed of their assignment.

Surgical technique

All patients underwent a routine open myomectomy performed by one of three operators (Alex Taylor, Adam Magos or Marcus Setchell) based on the technique described by Buttram and Reiter³. The default skin incision was a suprapubic transverse one. The uterus was exteriorised and the bowels packed away using two large wet swabs. We tried to use a single midline anterior uterine incision whenever possible. Blood loss was assessed by weighing swabs and measuring blood collected by suction. To calculate the amount of blood lost in the surgical swabs the following formula was used:

$$(\text{Wet swab weight (g)} - \text{dry swab weight (g)}) / 10.06 \text{ g/ml (the density of blood)}$$

The volume of blood measured by the suction was recorded in millilitres.

Suction drains were left inside for 48 hours. All patients received perioperative thromboprophylaxis with anti-embolic stockings and heparin, and antibiotic prophylaxis with co-amoxiclav (Augmentin®, GlaxoSmithKline).

Triple tourniquets

Three tourniquets were applied prior to myomectomy, one to occlude the uterine arteries and two more to occlude the left and right ovarian vessels. The broad ligament was opened anteriorly and the bladder reflected inferiorly. Next, a small opening was made in the avascular space in the posterior leaf of the broad ligament on either side of the uterine isthmus superior to the uterine vessels and ureter. A number 1 polyglactin tie was threaded through the two holes and tied tightly anteriorly around the cervix at the level of the internal os, using a Roeder slipknot, which could be retightened using a laparoscopic knot pusher if required.

A 20 cm length of narrow bore plastic tubing (we used a 3 mm Westcott® anaesthetic anti-syphon set) was used for the ovarian tourniquets based on the technique described by Thompson ¹⁰⁴. The tubing was passed through the defect in the broad ligament and looped around the infundibulopelvic ligament lateral to the fallopian tube and ovary. The two ends of the tubing were threaded through a short length of 24 Fr Foley catheter tubing, which acted as a cushion, and pulled tight and held with a small clamp to occlude the ovarian vessels. The procedure was repeated on the contralateral side

Control group

Women in the control group did not receive tourniquets.

Outcome measures

Primary outcome

- Intra-operative blood loss

Secondary outcomes

- Post-operative blood loss (assessed by surgical drains and changes in haemoglobin concentration)
- Blood transfusion rates
- Operative morbidity

Statistics

Data was analysed using t test (paired and unpaired), Mann-Whitney test, Wilcoxon signed rank test, and Fisher's exact test. The analysis was performed GraphPad Prism ® 4 software (GraphPad Software, San Diego California, USA) and SPSS® 11 software (SPSS Software, Chicago, Illinois, USA). We assumed significance at the 5% level ($p < 0.05$).

Results

The 28 patients were recruited from a cohort of 171 patients referred to hospital for management of moderately enlarged uterine fibroids. Of the 30 women for whom open myomectomy was judged appropriate, one patient was excluded because of anaemia due to thalassemia, and another declined to be

randomized (figure 13). The two-randomization groups were similar in baseline characteristics, including uterine size (Table 2).

Primary outcome

- *Intra-operative blood loss*

The operative details are summarised in Table 3. All myomectomies were completed successfully. Operating times were not significantly different between the two groups ($p=0.74$). The mean time the ovarian tourniquet was applied for in the tourniquet group was 52 minutes (range 26 to 77 minutes). Intra-operative bleeding was 1870 mls greater in the control group compared with those given tourniquets (95% CI 1159-2580 mls, $p<0.0001$).

Secondary outcomes

- *Blood transfusion rates, post-operative blood loss (assessed by surgical drains) and operative morbidity*

The transfusion rate in the control group was 79% compared to 7% in the tourniquet group ($p=0.0003$) (Table 4). Postoperatively, there were no statistically significant differences in pelvic drainage between the two groups at 20 minutes and 48 hours. Morbidity in the control group was significantly greater (8 versus 1 episodes, $p=0.0128$), especially the incidence of pyrexia $> 38^{\circ}\text{C}$ (Table 5).

Discussion

For the first time under controlled conditions, this study shows that triple tourniquets applied to the uterine and ovarian vessels significantly reduce operative blood loss, the need for blood transfusion and perioperative morbidity at open myomectomy. Although the study did not find a statistically significant benefit to leaving the absorbable uterine tourniquet in situ after the myomectomy, this was not a primary end point and the study proved underpowered for this outcome. The study was inclusive rather than exclusive and by including patients who had undergone previous laparotomy, including previous myomectomy, these results are as generalisable as possible.

Temporary haemostatic occlusion of the uterine blood supply at open myomectomy was first achieved using metal clamps⁶⁸ and evolved from earlier practices of caustic packs¹⁰⁵ and ligation of the uterine arteries¹⁰⁶. In the original description, both the uterine arteries and the ovarian vessels were occluded and although there are reports of occluding only the uterine arteries⁷⁸, the technique of total vascular occlusion of the uterine blood supply is still taught today¹⁰⁴.

Chemical tourniquets using vasopressin have also been described^{74;76}. One randomized trial comparing intramyometrial vasopressin with uterine tourniquet did report a significant advantage to the former, but ovarian tourniquets were not applied, the uterine tourniquet was released every 20 minutes, and most importantly, blood loss in swabs were not included in the estimation of operative blood loss⁷⁴. Another trial utilised occlusion of

both the uterine and ovarian vessels and reported no difference compared with vasopressin ⁷⁶. It seems, therefore, that triple tourniquets are effective as vasopressin injection, but without the risks of the latter to the extent that the use of vasoconstrictors at myomectomy is banned in some European countries ^{89;107;108}.

Whilst intra-operative blood loss in the tourniquet group was broadly comparable to previously published data, the results in the control group were considerably in excess of what I expected based on a review of the literature. One explanation could be the use of different methods of blood loss collection and estimation as discussed earlier. Another reason for this discrepancy might be differences in the amount of fibroid tissue removed. Previously published series do not include data on the weight of fibroids removed, and yet it is known that estimation of uterine size is only a rough estimate of uterine weight and therefore fibroid weight. One study, for instance, found that a uterus which on bimanual examination feels equivalent to an 20 week gestation has on average weight of about 1000g, but with a standard deviation of over 500g ¹⁰⁹. As intraoperative bleeding is proportional to the amount of fibroid tissue removed, differences in fibroid weight can account for major differences in blood loss data ⁷⁶.

In our study, pre-operative GnRHa was only used under certain well-defined conditions. Although such pre-treatment has been shown to be effective in reducing blood loss at open myomectomy ⁹³, these drugs are expensive, are associated with estrogen deficient side effects, can make the surgery more

difficult by causing fibrosis between the tissue planes, and most importantly, have been shown to be associated with an increase in fibroid recurrence at six months ⁹³. Recently the use of misoprostol as a pre-operative medical agent has been described but this technique requires further evaluation ¹¹⁰.

The use of an absorbable tourniquet that is left in situ around the uterine arteries to reduce perioperative bleeding and subsequent pelvic adhesions, is a novel idea and is potentially superior to the recently reported techniques of permanent bilateral ligation of the ascending branches of the uterine artery ^{79;80;87}.

In one these groups, the investigators cut and ligated the uterine artery with 2.0 vicryl^{79;80}. In the other group investigators, either permanently tied off the uterine arteries with silk sutures at laparotomy or occluded them with hemoclips at laparoscopy. All of these methods appeared to reduce intra-operative blood loss. However because they are permanent, their use like UAE in women who wish to preserve their fertility is of concern. Despite this recently reported two year data suggests that permanent ligation leads to improved long term results and less fibroid recurrence ¹¹¹. In addition a number of successful pregnancies were also reported.

The absorbable tourniquet in theory should have less effect on subsequent fertility. Longer term follow up is required to assess its effect on fibroid recurrence. That it did not significantly reduce post-operative bleeding may be because the study was underpowered to examine such an outcome. It could also be that the use of drain volumes is a crude outcome measure against which to evaluate the tourniquet as it reflects not only blood loss but serous

fluid that oozes from the uterine incisions and therefore potentially might be erroneous.

Figure 13. Trial Profile

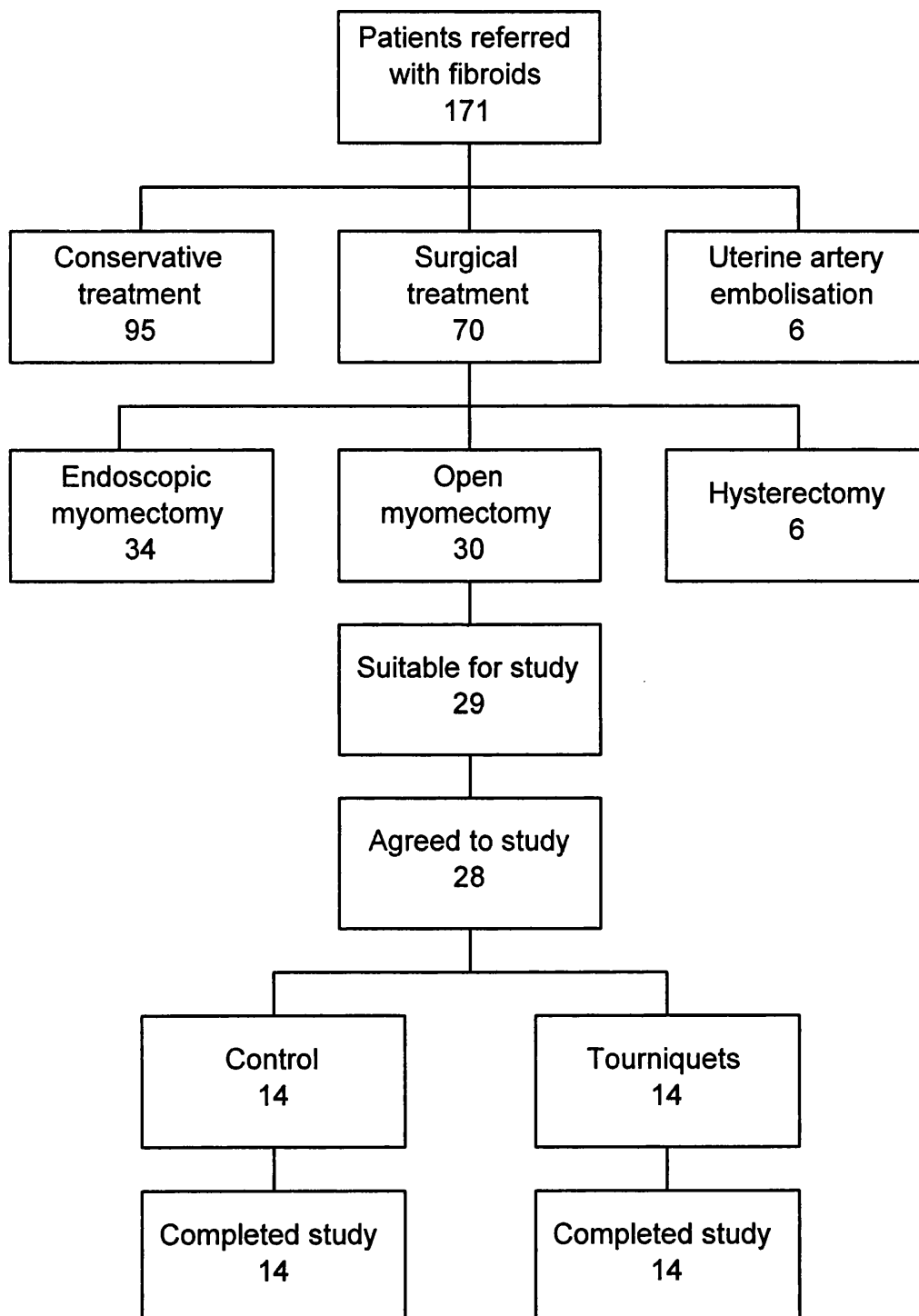


Table 2. Patient baseline characteristics

	CONTROL GROUP (N=14)	TOURNIQUET GROUP (N=14)
Age (years)	39.5 (SD 4.7)	42.6 (SD 6.7)
Parity	0 (0 to 3)	0 (0 to 3)
Pre operative Hb (g/dl)	11.8 (SD 0.7)	12.2 (SD 0.9)
GnRHa	1	2
Previous surgery	2	3
Uterine Size	18 (SD 3.7)	17 (SD 2.4)
Mean number of fibroids	2.6 (1 to 4)	2.9 (1 to 4)
Cases of multiple fibroids(>5)	2	3
Mean diameter of largest fibroid (cm)	7.7 (SD 2.5)	8.4 (SD 2.9)

Table 3. Operative details

	CONTROL GROUP (N=14)	TOURNIQUET GROUP (N=14)	P
Transverse/Vertical incision	12/2	14/0	0.48
Operating time (mins)	118 (SD 40)	114 (SD 27)	0.74
Tourniquet time (mins)	-	52 (SD 17)	-
No. fibroids removed	4.5 (1 to 34)	10.5 (1 to 24)	0.35
Weight fibroids (g)	481 (SD 330)	395 (SD 246)	0.44
Blood loss (ml)	2359 (SD 1241)	489 (SD 362)	<0.0001

Table 4: Postoperative blood loss and transfusion data

	CONTROL GROUP (N=14)	TOURNIQUET GROUP (N=14)	P
Drain at 20 mins (ml)	20 (5 to 120)	15 (0 to 40)	0.167
Total drain at 48 hours (ml)	220 (70 to 320)	150 (0 to 420)	0.165
Hb drop pre-op to day 2 (g/dl)	2.96 (SD 0.92)	2.79 (SD 0.33)	0.79
No. patients transfused	11 (79%)	1 (7%)	0.0003
<i>Blood</i>	<i>59 units</i>	<i>2 units</i>	<i>0.0005</i>
<i>Fresh frozen plasma</i>	<i>21 units</i>	<i>0</i>	<i>0.016</i>
<i>Platelet</i>	<i>2 unit</i>	<i>0</i>	<i>0.48</i>

Table 5. Postoperative morbidity

	CONTROL	TOURNIQUET	P
Total morbid events	8 *	1	0.0128
Pyrexia > 38 degrees C	5	0	
Post-op haemorrhage	1	0	
Repeat surgery	1	0	
Bowel obstruction	1	0	
Wound infection	0	0	
Wound haematoma	0	1	
Chest infection	0	0	
DVT	0	0	

* Involved 5 patients

Chapter Five: A feasibility study of triple tourniquets at laparoscopy myomectomy

Introduction

Fibroids are associated with menorrhagia, pelvic pressure symptoms and infertility. Laparoscopic myomectomy, preserves fertility, is associated with less analgesia requirement and a shorter inpatient stay^{3,4}. However, as at open myomectomy bleeding can be considerable. Hemostatic techniques at open surgery are well described but surgical options at laparoscopy are limited.

We have recently described the use of a novel absorbable cervical tourniquet at open myomectomy⁵. Here we report our use of it during laparoscopic myomectomy.

Patients and Methods

Women with symptomatic uterine leiomyoma who were judged to be suitable for laparoscopic myomectomy were recruited from the Fibroid Clinic at the Royal Free Hospital, London between May 2002 and May 2003. Inclusion criteria included a wish to retain their fertility, and uterine size less than or equal to a 14 week gravid uterus on clinical examination. Exclusion criteria included women with mainly intra-cavity myomas, pedunculated subserous myomas, a history of a bleeding disorder, concurrent anticoagulant therapy, haemoglobin less than 10.5 g/dl and previous myomectomy. The study protocol was approved by the Local Ethics Committee (Application No. 5855).

Pre- and post-operative assessment

All women underwent pre-operative ultrasonography to assess the site and size of the fibroids. Five women received 3 months pre-operative treatment

with Goserelin (Zoladex ®, Astra Zeneca, London, UK) either to reduce the size of their fibroids, or to correct anaemia. All patients were given prophylactic antibiotics during and for 5 days after surgery (typically Augmentin ®, GlaxoSmithKlein, Uxbridge, UK).

Surgical Technique

A standard 4-port laparoscopy was performed under CO₂ pneumoperitoneum using a subumbilical or left upper quadrant port for the laparoscope, a 10mm port in the left lower quadrant (ipsilateral side to the surgeon), and two 5mm ports placed suprapubically and in the right lower quadrant respectively. The uterovesical fold was opened and the bladder identified. A long No. 1 polyglactin tie was introduced on a pointed grasper via the suprapubic port and threaded around the cervix through small incisions in the avascular space, in the broad ligament on either side of the uterine isthmus immediately lateral and superior to the uterine vessels. The suture was brought out through the suprapubic port and tightened anteriorly on to the cervix using an extracorporeal Roeder knot to occlude the uterine vessels (Figure 14). The suture was left long so that the Roeder knot could be retightened if required.

An additional number 1 polyglactin tie was inserted via the suprapubic port, passed through the incision in the left broad ligament and carried under the Fallopian tube and ovary before being brought out through the left lower quadrant port. The other end of the tie was pulled into the peritoneal cavity and also brought out through the left lateral port so that this pedicle included the infundibulo-pelvic and round ligaments, with the ovary, fallopian tube and

ovarian ligament lying medial to the tourniquet. A Roeder knot was then tied to occlude the left ovarian vessels within this pedicle, and cut 3 cm from the knot so that it could more easily be removed at the end of the myomectomy. The procedure was then repeated on the contralateral side to occlude the right ovarian blood supply (Figure 15).

With all three tourniquets in place, a laparoscopic myomectomy was then carried out using bipolar desiccation and blunt and sharp dissection to excise the myoma(s) (Figures 16 & 17). The uterine incision(s) were carefully repaired in layers before cutting the ties around the infundibulopelvic ligaments. The uterine artery tourniquet was retightened at the end of the surgery and cut short, leaving it in situ to dissolve over the next few weeks. The excised fibroids were removed by morcellation or via a posterior colpotomy, and a size 10 Redivac® drain left in before deflation and closure of the abdominal wall incisions.

Postoperative care

Postoperative management was routine. Haemoglobin estimation was repeated on the second postoperative day. Patients were discharged from hospital when medically fit and reviewed 6 weeks after surgery.

Outcome measures

Primary outcome measure

- Intra-operative bleeding*

Secondary outcome measures

- Blood transfusion rates
- Post-operative blood loss (assessed by pelvic drains)
- Operative morbidity

* Blood loss was estimated by meticulous collection all suction fluids. To take account of the use of irrigation fluid (Normal Saline), the actual blood loss was calculated from the dilution of haemoglobin in the suction reservoir compared to the pre-operative haemoglobin.

Results

During the study period, a total of 171 patients were seen in the Fibroid Clinic, and 70 underwent myomectomy (open myomectomy 30, laparoscopic myomectomy 13, hysteroscopic myomectomy 21). Of those treated laparoscopically, 10 were done using triple tourniquets while the three patients with single, pedunculated myomas were managed without.

The average age of the patients was 38 years (29-45), and their parity 1 (0-2). Nine were Caucasian and one was Afrocarribean. Nine women had had no previous surgery while one had undergone a lower segment caesarean section. The median uterine size was equivalent to 12.4 weeks gestation (range 8-14). Pre-operative ultrasound assessment identified an average of two fibroids per patient (range 1-10), ranging in diameter from 3.8 to 9.8 cm (median 6.8). The myomas were intramural in six cases, and intramural and subserosal in four.

All procedures were completed successfully by the intended route. An average of 2 fibroids were removed per patient (range 1-10), with a median total weight of 209 g (range 22-290). Total operating time ranged from 100 to 265 mins (median 178), the ovarian tourniquet being applied for an average of 71 mins (range 45-158). Measured intra-operative blood loss averaged 163 ml (range 33-827). Post-operatively, the median loss in the pelvic drain at 20 minutes was 20 mls (range 10-280), and at 24 hours 248 ml (range 90-430). The average drop of the day 2 haemoglobin was 2 g/dl (range 0.7-4.9). In the learning phase of the technique, one patient received a two-unit blood transfusion having sustained a vessel injury in the broad ligament during insertion of the right ovarian pedicle suture. There were no other complications.

Discussion

Surgical techniques to reduce blood loss at open myomectomy are well described and include myomectomy clamps⁶, tourniquets^{7,8,9} and vasoconstrictor agents¹⁰. Haemostasis at laparoscopic myomectomy can be just as challenging as at open surgery with the caveat that this route of surgery tends to be reserved for the smaller uterus with fewer fibroids. When first described in the late seventies, bleeding at laparoscopic myomectomy was minimized by injecting a vasoconstrictor into the myometrium¹¹. Whilst vasoconstrictor agents are effective¹², as has already been mentioned, they are not without risks. Similarly, there are advantages and disadvantages to

medical pre-operative treatment with gonadotrophin releasing hormone analogues (GnRHa) as discussed earlier.

In theory, occlusion of the uterine blood supply with tourniquets to create a “dry” surgical field should be possible at laparoscopic myomectomy as it is open myomectomy. Temporary occlusion of the uterine isthmic vessels with a number 0-Polydioxanone (PDS) Endoknot has recently been reported with promising results ¹⁵. However, the blood supply to the uterus comes not only from the uterine artery but also from the anastomosis with the ovarian vessels, and this is the reason why occlusion of both the uterine and ovarian blood flow to the uterus is an established technique at laparotomy ⁷. We applied the same principles to laparoscopic myomectomy, and our feasibility study shows that such temporary devascularisation can be applied successfully at laparoscopy as well.

The procedure differs from the traditional laparotomy tourniquet technique in that an absorbable tourniquet was tied around the uterine vessels, and not removed at the end of surgery but left *in situ* to dissolve over the ensuing weeks. (See previous section on open myomectomy study). As our study was uncontrolled, we do not know if the use of absorbable tourniquets at laparoscopy reduces the morbidity of myomectomy as they do at laparotomy, but significant postoperative bleeding did not occur in any of our patients. Following the case of the one patient who was transfused, the technique has been slightly modified, and the surgeon is now careful to reflect the anterior

leaf of the broad ligament to ensure visualisation of an avascular space in the posterior leaf through which the tourniquet can be passed.

figure 14 Uterine artery tourniquet at laparoscopic myomectomy

A- Straight knot pusher tightening uterine artery tourniquet

B- Opened uterovesical fold

C- Cervix

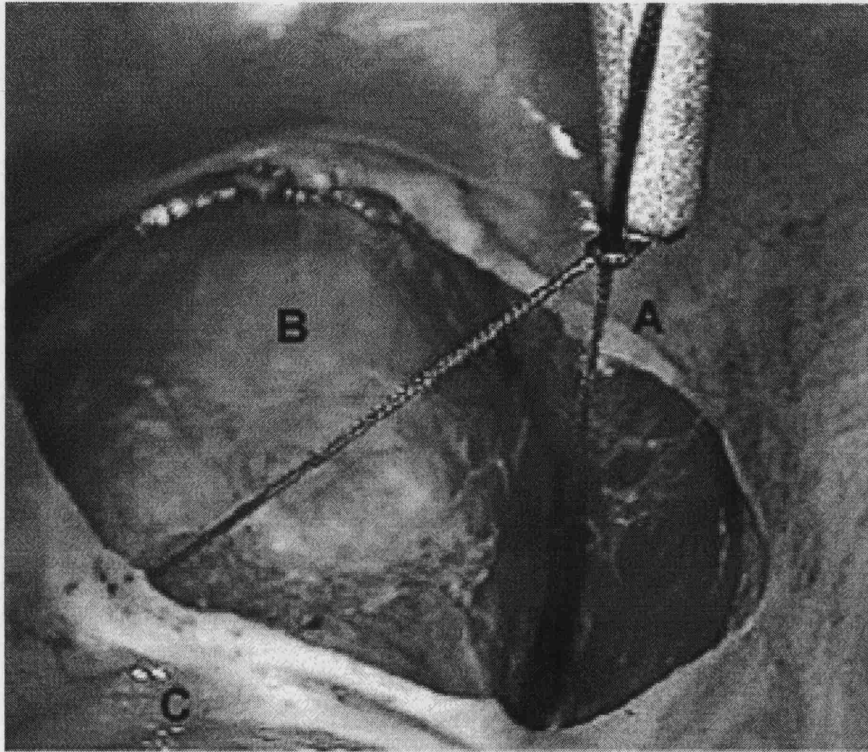


figure 15 Right ovarian tourniquet at laparoscopic myomectomy

A- Application of right ovarian tourniquet

B- Right ovary and tube, held medially prior to tightening of tourniquet

C- Uterus

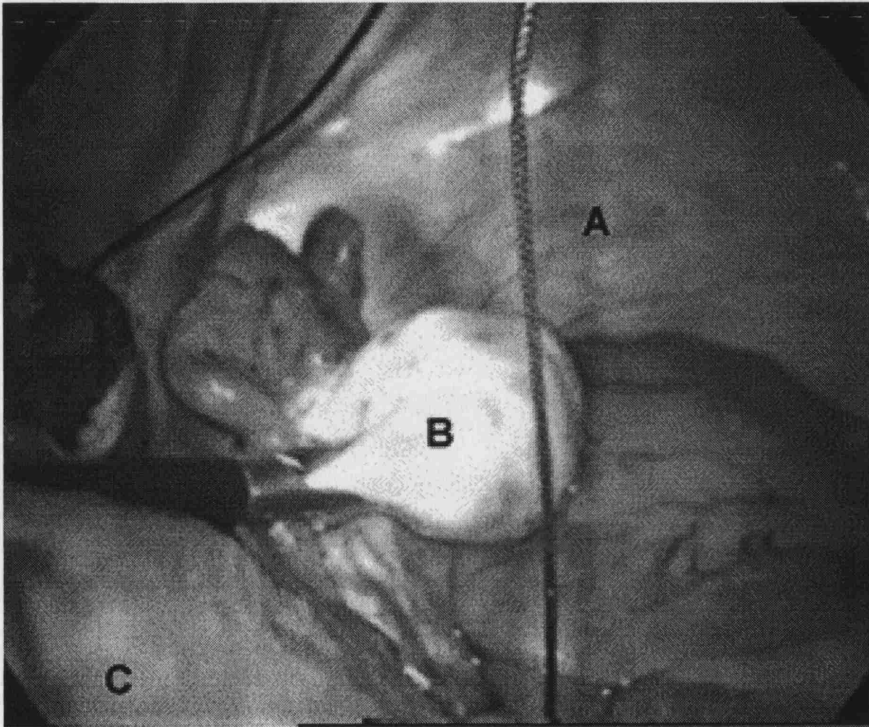


figure 16 Triple tourniquets in place at laparoscopic myomectomy

A- Uterine artery tourniquet

B- Left ovarian tourniquet

C- Right ovarian tourniquet

D- Opened uterovesical fold exposing cervix

E- Uterus

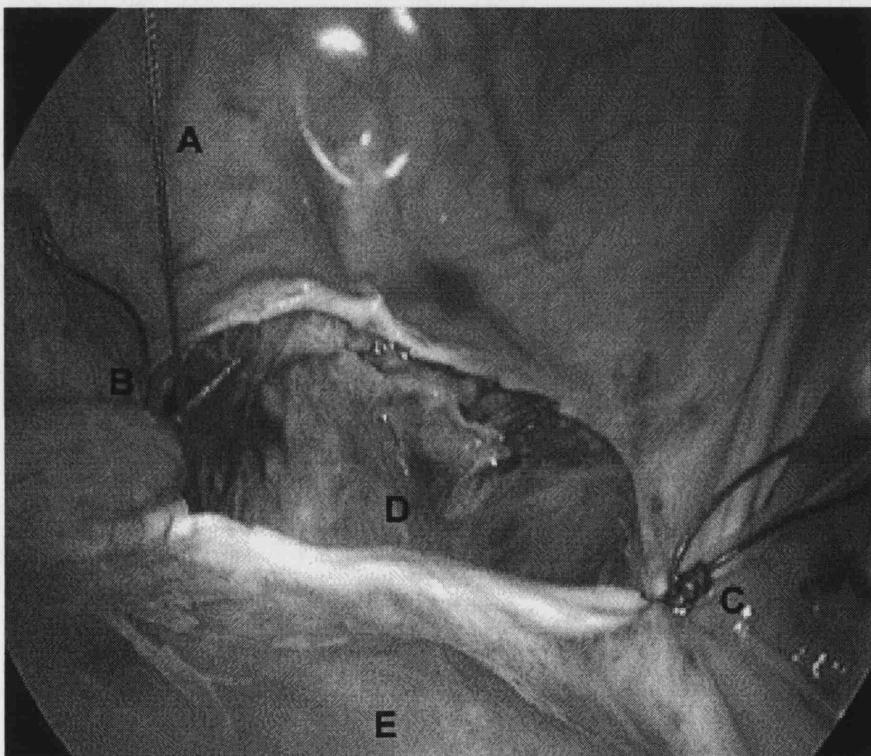
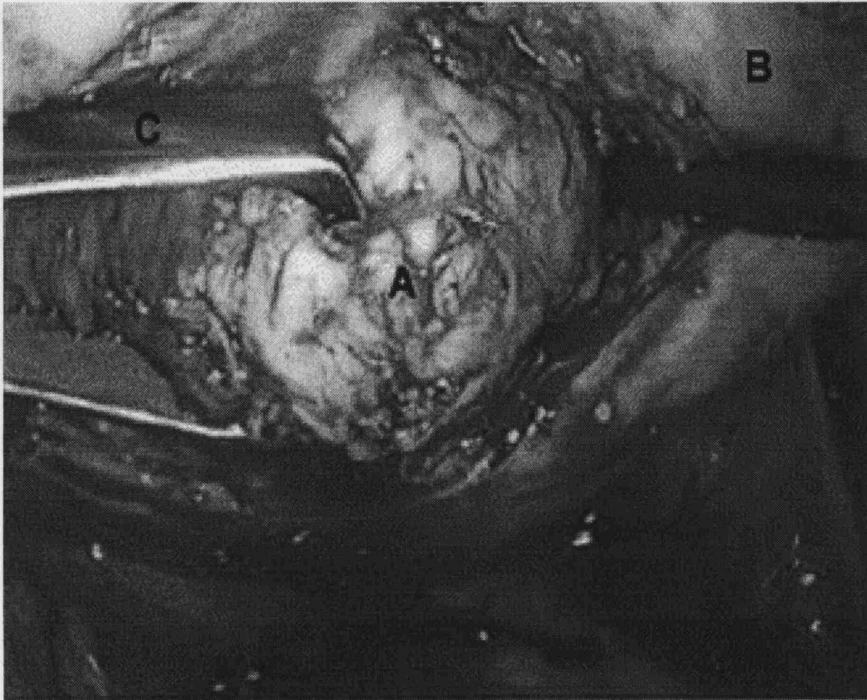


figure 17 Excision of fibroid at laparoscopic myomectomy

A- Dissection of fibroid

B- Uterus

C- Claw forceps



Chapter Six: The effect of tourniquets on uterine blood flow

Introduction

The evaluation of uterine and ovarian haemodynamics post uterine artery embolisation (UAE) is well reported ^{62;113;114}. But data on uterine perfusion post myomectomy is sparse ¹¹⁵, with no data in the literature on serial measurements post open myomectomy. Our data for the first time uses Doppler ultrasound to assess the effect of myomectomy on uterine artery blood flow and to assess the effect on the haemodynamic changes associated with a novel absorbable cervical tourniquet.

Patients and methods

From January 2002 to July 2003, patients seen in the Fibroid Clinic and Gynaecology Clinic were assessed for entry into a randomised controlled trial, evaluating the use of tourniquets as a haemostatic technique to reduce blood loss at open myomectomy and in particular the use of an absorbable polyglactin tie (cervical tourniquet) left in situ at the end of the operation. The main outcome measure was intra-operative blood loss which is reported in Chapter Four. However we were also interested in assessing the effect on uterine artery blood flow post-operatively. It is this data that is presented here. The trial design has already been described in detail in Chapter Four, but it is worth reiterating the relevant points in relation our study of uterine blood flow. All patients underwent a routine open myomectomy. In the tourniquet group, three tourniquets were applied prior to myomectomy, one to occlude the uterine arteries and two more to occlude the left and right ovarian vessels. To occlude the uterine arteries, a number 1 polyglactin tie was tied tightly anteriorly around the cervix at the level of the internal os using a Roeder

slipknot, which could be retightened using a laparoscopic knot pusher if required. This remained insitu at the end of the operation. For the ovarian tourniquets we used a 20 cm length of 3mm plastic anti-syphon tubing. The tubing was passed through the broad ligament and looped around the infundibulopelvic ligament lateral to the fallopian tube and ovary. The ovarian tourniquets were released at the end of the procedure.

All patients were scanned with a Type HDI 3000 Philips ATL scanner (Eindhoven, Netherlands) equipped with a C8-4 MHz trans-vaginal probe. Colour Doppler sonography was used to identify the uterine artery just lateral to the cervix. The resistance index (RI), pulsatility index (PI) and peak systolic velocity (PSV) were then calculated from the flow velocity waveforms of both uterine arteries. Care was taken to ensure that angle correction was applied when measuring PSV. To optimise flow imaging and to eliminate noise and aliasing adjustments were made to the pulse repetition frequency, wall filter and sample volume size. Doppler measurements were obtained pre-operatively and post-operatively at day 5, 6 weeks, 3 months and 6 months. All Doppler measurements were performed by one of the researchers (S.B). The day of the cycle was not considered when performing the ultrasound assessments.

Pre-operative gonadotropin releasing hormone agonists (GnRHa) were only prescribed if the patient was anemic ($Hb < 10.5$ g/dl) or if uterine size was > 20 weeks gestation size (to facilitate the use of a low transverse incision at myomectomy). The study protocol was approved by the Royal Free Hospital,

Local Ethics Committee (Application No. 5855) and written informed consent was obtained from all participants.

Statistics

Data was analysed with independent sampled t test and paired t test using SPSS® 11 software (SPSS Software, Chicago, Illinois, USA). We assumed significance at the 5% level ($p < 0.05$).

Results

Of the 28 patients (14 in each group) who underwent open myomectomy, data was obtained for 12 patients in the tourniquet group and 11 in the control group. Three patients did not attend for their pre-operative Doppler assessment and one patient in each group did not subsequently attend for follow up measurements.

The two-randomization groups were similar in baseline characteristics, including uterine size, number of fibroids and size of fibroids (Table 2). Where there were more than five fibroids, the uterus was reported as containing "multiple fibroids". Therefore when the mean number of fibroids was calculated, these uteri were excluded from the analysis.

RI, PI and PSV values were calculated for both right and left arteries. There were no significant differences between the two vessels (figures 18-20) and so for ease of data interpretation, the following results relate only to the right

uterine vessel indices. . There were no differences between the two groups for either uterine artery Doppler resistance indices at 5 days ($p=0.70$), 6 weeks ($p=0.17$), 3 months ($p=0.40$), 6 months ($p=0.41$) post-operatively (figure 18a & b) or for pulsatility indices at 5 days ($p=0.62$), 6 weeks ($p=0.53$), 3 months ($p=0.70$), 6 months ($p=0.38$) post-operatively (figure 19a & b). However the peak systolic velocity (PSV) was significantly reduced in the tourniquet compared to the control group at 5 days ($p=0.014$). Thereafter there were no significant differences in the PSV between groups at 6 weeks ($p=0.44$), 3 months ($p=0.07$), or 6 months ($p=0.53$) (figure 20a & b).

Discussion

Ultrasound imaging was first used in gynaecology in the 1950's ¹¹⁶. Since then it has been developed and refined almost beyond all recognition. It is now widely used throughout medicine and has become a routine extension of clinical examination. Doppler ultrasound is a more sophisticated version of basic ultrasound technology. It allows the assessment and analysis of a moving target and is therefore a very useful non-invasive tool in the evaluation of blood flow. The detailed physics of the Doppler equipment is beyond the scope of this thesis, but the basic principle is that of the Doppler effect. This can be explained as follows. When a source of sound waves and an observer are approaching each other the observed frequency of the sound is increased (the pitch/tone of the sound goes up). The explanation is that the observed frequency of sound depends upon the number of wavefronts reaching the ear per second. So the closer the source of sound to the observer, the more

wavefronts hit the ear, so the tone of the sound goes up. The shift between the emitted frequency and the observed frequency is called the Doppler effect. By directing an ultrasound wave (generated from a piezoelectric crystal, mounted in the transducer probe) at blood cells within vessels, this Doppler effect can be measured and displayed. This Doppler signal can then be analysed to reveal the underlying clinical condition of the vessel. Colour Doppler sonography is a non-invasive technique that can be used to assess blood flow. It is based on the assumption that red blood cell motion is the same as blood flow. The amplitude of each Doppler component corresponds to the number of red blood cells moving at a specific velocity and at a particular time. Flow away from the transducer is displayed in shades of dark blue, bright blue and blue-green. Different velocities also depicted by different colour shades. It was colour Doppler sonography that was used to locate the uterine artery. Once located the Doppler waveform of the uterine artery was acquired by means of pulse Doppler wave equipment.

The pulsatility index (PI) is the difference between the highest value of the waveform and the lowest value of the waveform divided by the mean value (figure 21). The A: B ratio describes the rate at which flow velocities fall away during diastole. It closely responds to peripheral resistance. The resistance index (RI) makes use of the same two points as the A: B ratio but expresses the values in a more convenient form. It is for that reason the RI index is reported rather than the A: B ratio. The peak systolic velocity is commonly used to assess arterial stenosis in peripheral vascular disease ¹¹⁷. As a general rule the greater the degree of arterial narrowing the higher the peak

systolic velocity, unless there is complete arterial occlusion, in which case there will be no flow (Table 6).

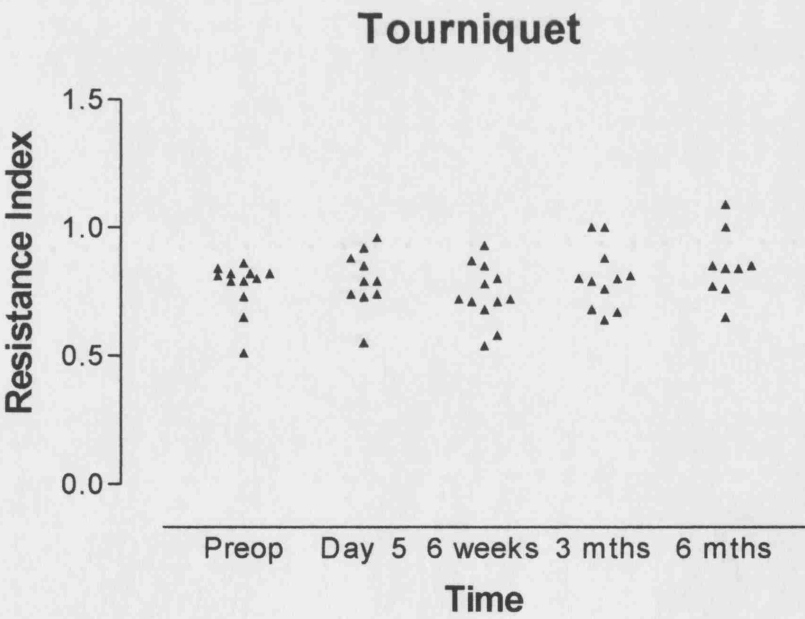
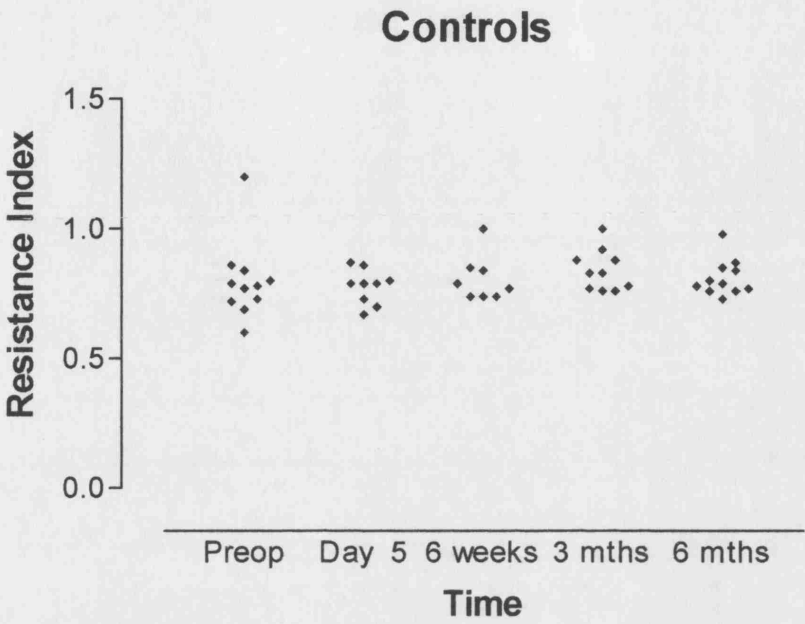
Polyglactin sutures are completely absorbed by slow hydrolysis at 60-70 days post operatively. However their tensile strength diminishes rapidly, such that only 40% remains at three weeks. We would therefore expect them to have a temporary effect on uterine artery blood flow (ie. post-operative haemostasis) before their tensile strength diminishes, facilitating a return towards normal reperfusion. Our PSV data clearly demonstrates this but surprisingly, we did not see a rise in PSV in all patients, as we would have expected at day 5. In some cases the tourniquet may have loosened, whilst in other cases we might well have sampled smaller collateral vessels, no longer being able to detect the occluded uterine artery. This later point is important, because occluding the main blood supply to the uterus might in theory put it at risk of being infarcted. The opening up of detectable collaterals is reassuring and is consistent with the many reported techniques of artery ligation to control obstetric haemorrhage^{79;118;119} and more recently with UAE⁵⁵.

The apparent lack of effect on the RI and PI is reassuring, but slightly surprising. RI and PI reflect vascular impedance, which in turn approximates resistance to arterial flow. These values are significantly increased following UAE. That they should not appear to be significantly affected by the cervical tourniquet may be explained by the fact that the tourniquet works from outside in rather than inside out as in UAE. That is to say the uterine artery lies within

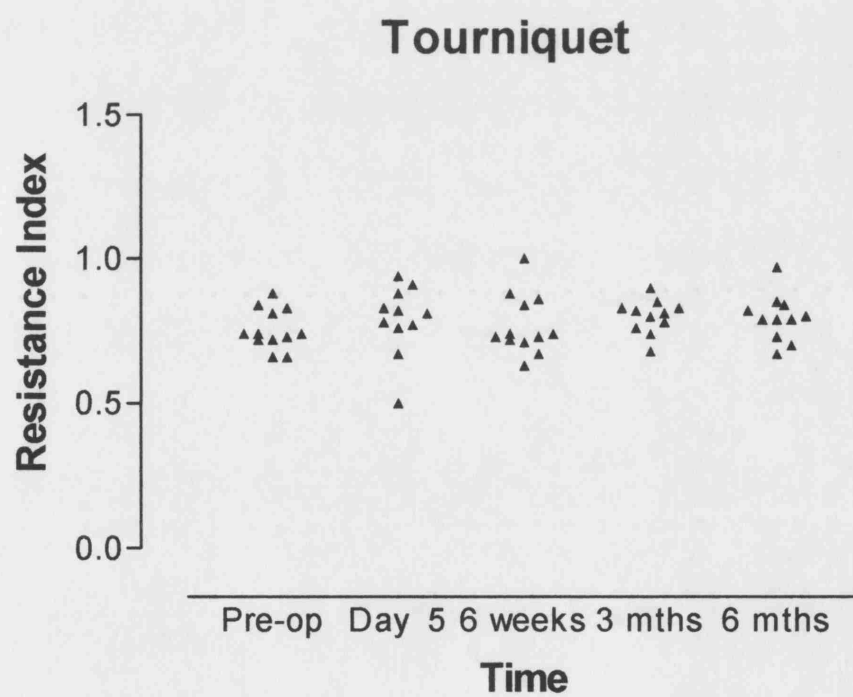
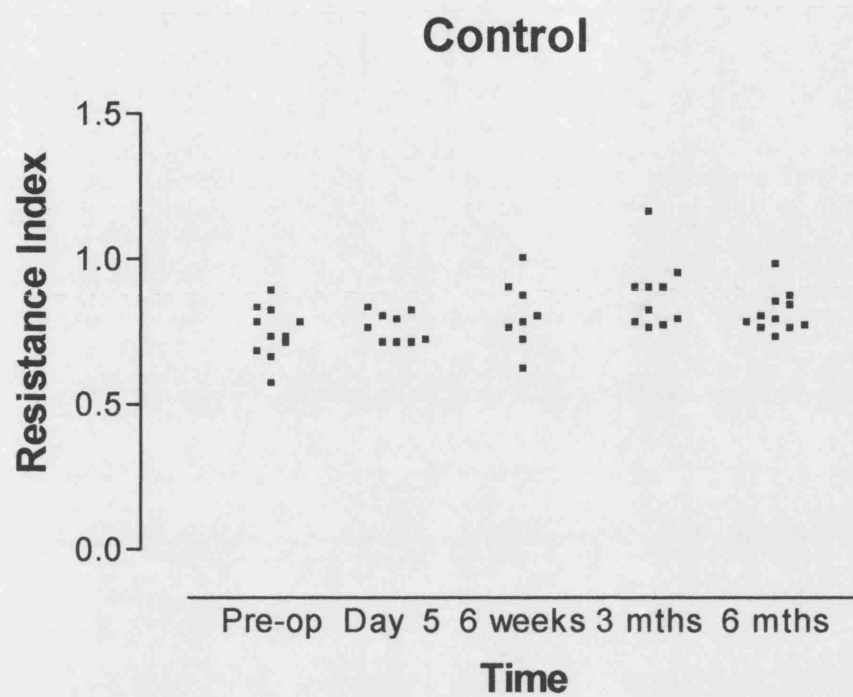
the connective tissue of the cervix and broad ligament, tissue that may modulate the effect of the tourniquet and therefore the RI and PI.

The use of tourniquets at open myomectomy is not new⁷⁸, but they are effective and our novel cervical tourniquet appears to reduce peri-operative ooze. Ultrasound Doppler evaluation of this technique suggests that there are no long- term harmful effects on uterine reperfusion.

figures 18a & 18b. Changes in right uterine artery Doppler resistance index



figures 18 c & 18d. Changes in left uterine artery Doppler resistance index



figures 19 a & 19b. Changes in right uterine artery Doppler pulsatility index

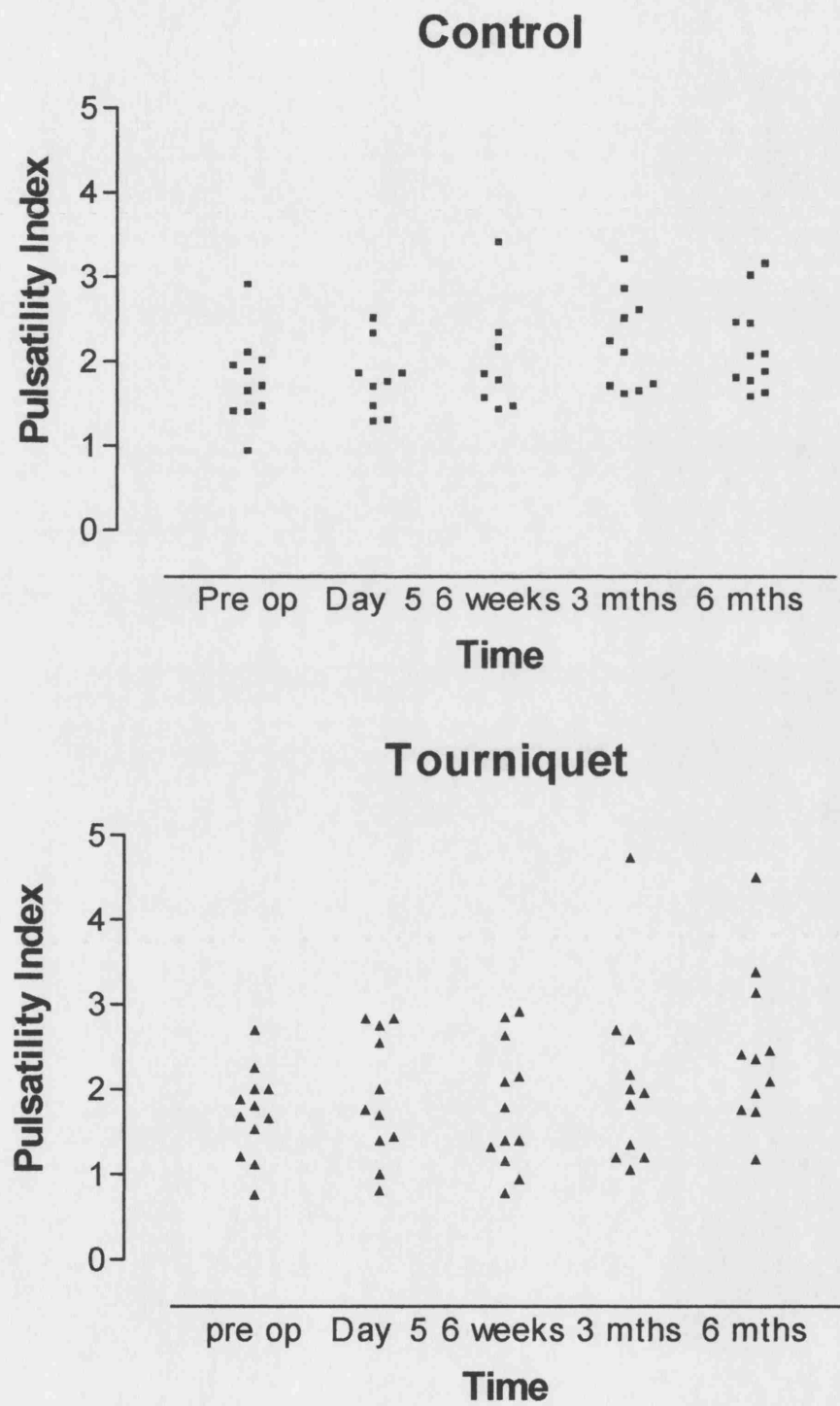


figure 19c & 19d. Changes in the left uterine artery Doppler pulsatility index

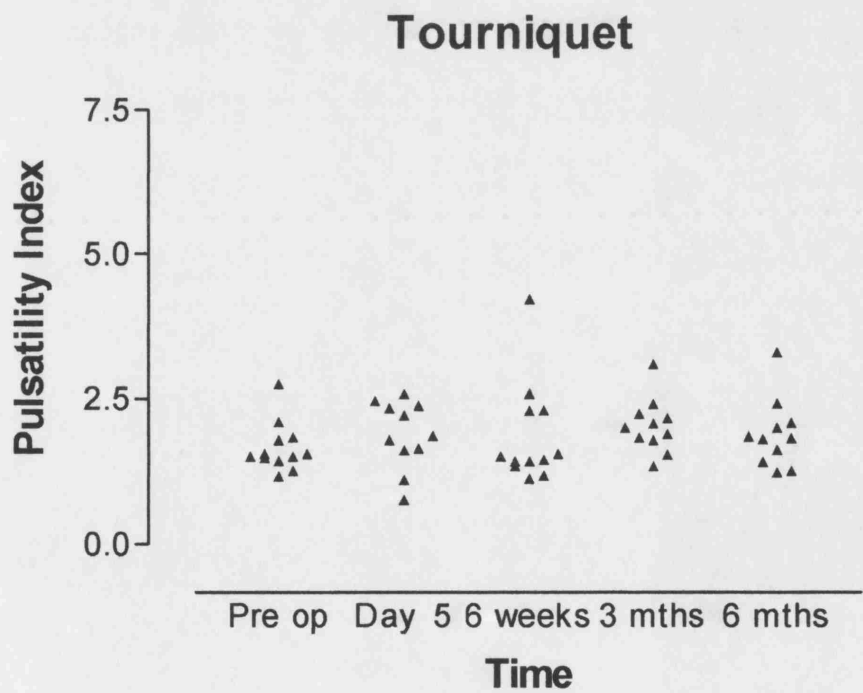
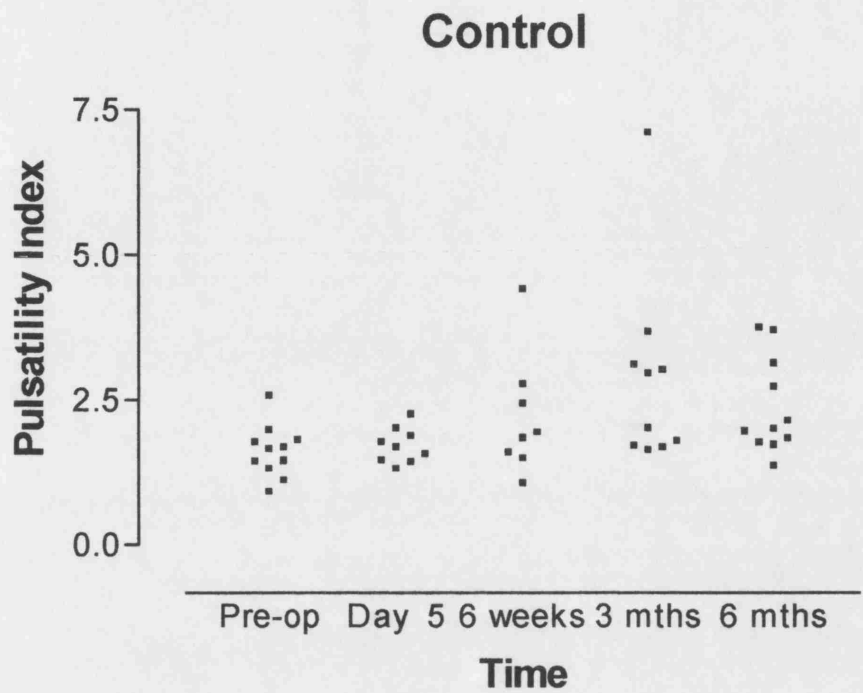


figure 20 a & 20b. Right uterine artery peak systolic velocity

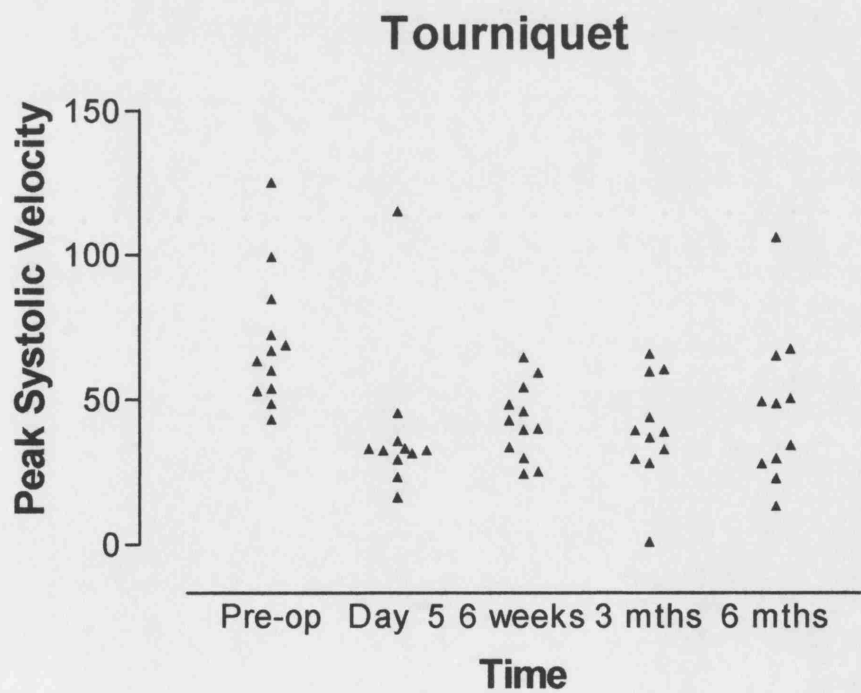
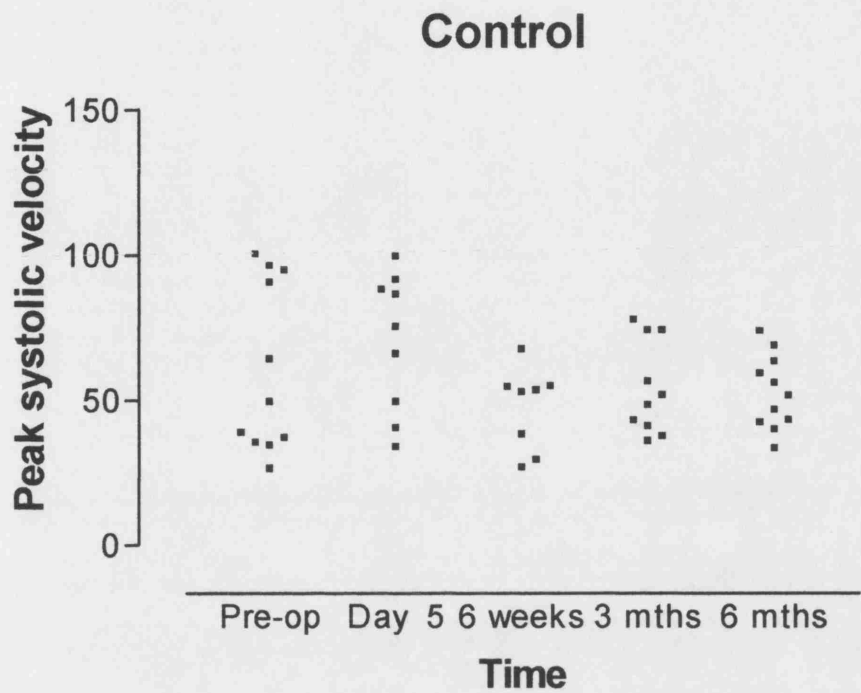


figure 20c & 20d. Left uterine artery peak systolic velocity

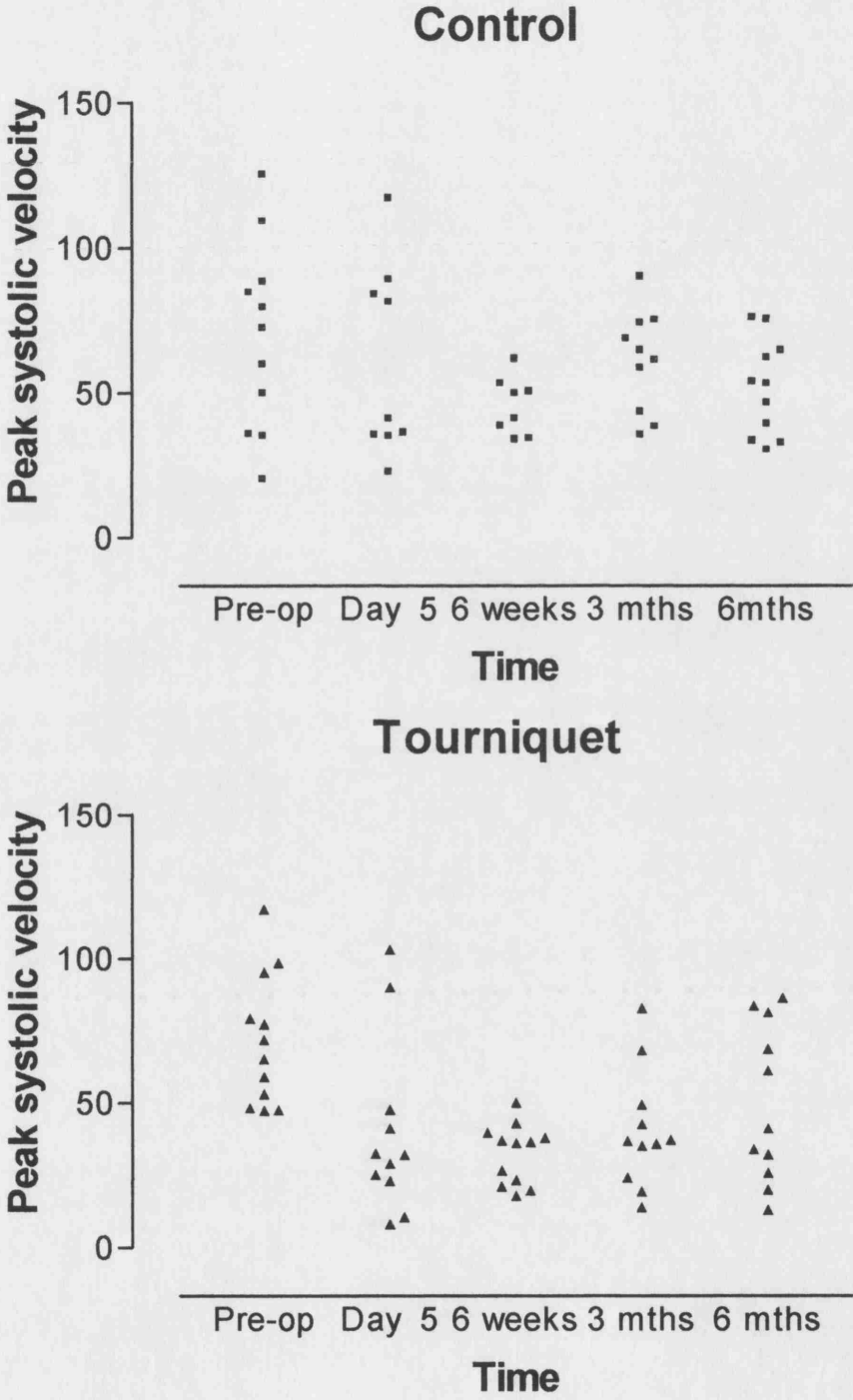
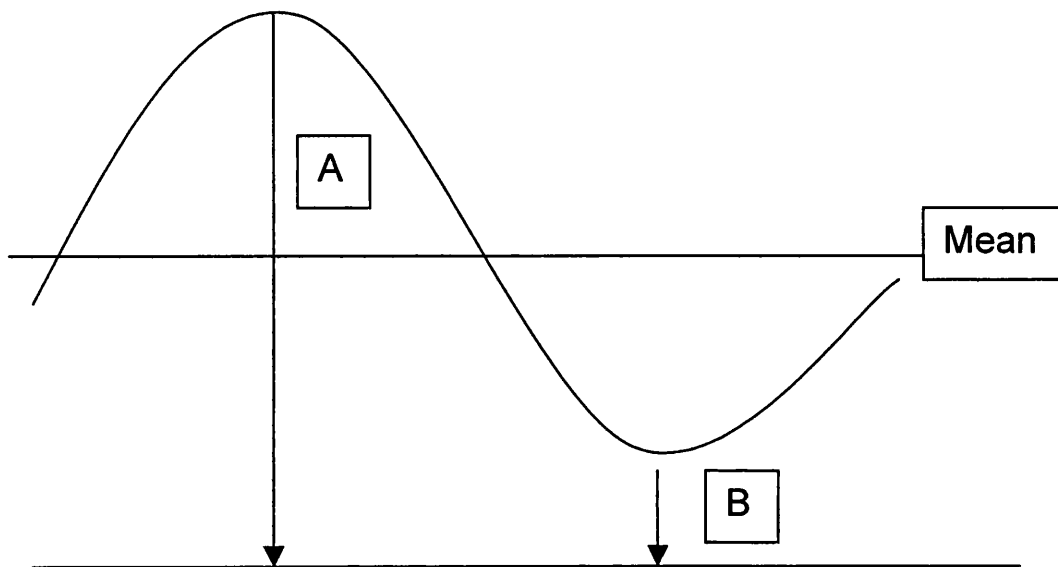


figure 21. A Schematic waveform showing how the common indices that are applied to the Doppler waveform are obtained



Pulsatility index (PI) = $A - B / \text{Mean}$

A/B ratio = A / B

Resistance index (RI) = $A - B / A$

Table 6. Relationship between peak systolic velocity and degree of stenosis

Diameter of Stenosis (%)	Peak systolic velocity (cm/s)
0-39	<110
40-59	110-149
60-79	150-249
80-99	250-610
100	0

Chapter Seven: The effect of tourniquets ovarian function

Introduction

In the original description of the use of tourniquets at myomectomy both the uterine and the ovarian arteries were occluded to create as “dry” a surgical field as possible ^{106;120}. Though this still remains standard teaching ¹⁰⁴, in theory occluding the ovarian blood supply may have harmful effects. On reviewing the literature, research in this area is either absent or unpublished. By contrast ovarian function post hysterectomy ¹²¹⁻¹²³ and post UAE ^{60;124} is well reported. Our tourniquet studies investigate this important outcome for the first time.

Patients and Methods

In both the open myomectomy RCT and the laparoscopic myomectomy pilot study (Chapters three and four), follicle stimulating hormone (FSH) levels were checked on day two of the cycle pre-operatively and again on day two of the cycle three months post-operatively.

Statistics

Pre- and post-operative changes in serum FSH concentrations were compared using Wilcoxon signed rank test for paired data. The analysis was performed using GraphPad Prism ® 4 software (GraphPad Software, San Diego California, USA. We assumed significance at the 5% level ($p < 0.05$).

Results

- *Ovarian function, assessed by changes in serum FSH*

Of the 28 patients in the open myomectomy RCT, complete data was obtained for 12 patients in the tourniquet group and for 11 patients in the control group. In the laparoscopic study data was obtained for five women, the remainder received pre-operative treatment with Goserelin (Zoladex®, Astra Zeneca, London, UK) either to reduce the size of her fibroids or to correct anaemia.

In the laparotomy RCT the mean time the ovarian tourniquet was applied for was 52 minutes (range 26 to 77 minutes). In the laparoscopy study the mean time the ovarian tourniquet was applied for was 71 minutes (range 45 to 158 minutes).

In the open myomectomy study, there were no significant differences in day two serum FSH concentrations at three months after surgery compared to baseline values in either the control or tourniquet group ($p=0.25$ and $p=0.41$ respectively) (Figures 22a & 22b). Similarly changes in day two serum FSH concentration were not statistically significant in the laparoscopic tourniquet study ($p=0.62$) (Figure 23)

Discussion

In the original reports of myomectomy, the ovarian blood supply was occluded with ring forceps. Concern about ovarian ischemia led to one surgeon placing a rubbershod clamp medial to the ovaries to preserve ovarian perfusion ¹²⁵.

This had a gap in the clamp jaws to prevent tubal injury, but importantly still occluded the blood supply to the uterus via the round ligament (Sampson's artery). However the placement of such clamps can hamper and impede the myomectomy. As a result, this reported technique is rarely used.

For the first time this trial attempted to determine the effect of triple tourniquets on ovarian function based on changes in serum FSH, the rationale being that ischaemic injury might result from the application of the tourniquets, depleting the ovarian reserve and therefore secondarily causing a rise in FSH. Although the mean tourniquet time was close to one hour in the open myomectomy study and seventy minutes in the laparoscopic myomectomy study, reassuringly there did not appear to be any significant changes observed compared to pre-operative levels. However I accept the study might not have been appropriately powered to detect a difference. The results though are in keeping with data from heterotopic autotransplantation in the ewe (an accepted model in reproductive endocrinology) which suggests that there is only minimal injury to ovarian tissue even after three hours of ovarian vascular occlusion ¹²⁶.

It could be argued that FSH alone is sufficient to assess ovarian function. Investigators examining fertility in cancer survivors have used a range of biochemical indices, estradiol, inhibin B and anti-Mullerian hormone (AMH) in addition to FSH ¹²⁷. However none of these indices at the moment have been shown to predict ovarian reserve accurately. It would be prudent to recommend an appropriately powered study be carried out in the future to

answer this specific question, although choosing which biochemical indice to use, remains controversial.

figures 22a & 22b. Changes in serum FSH in Laparotomy RCT

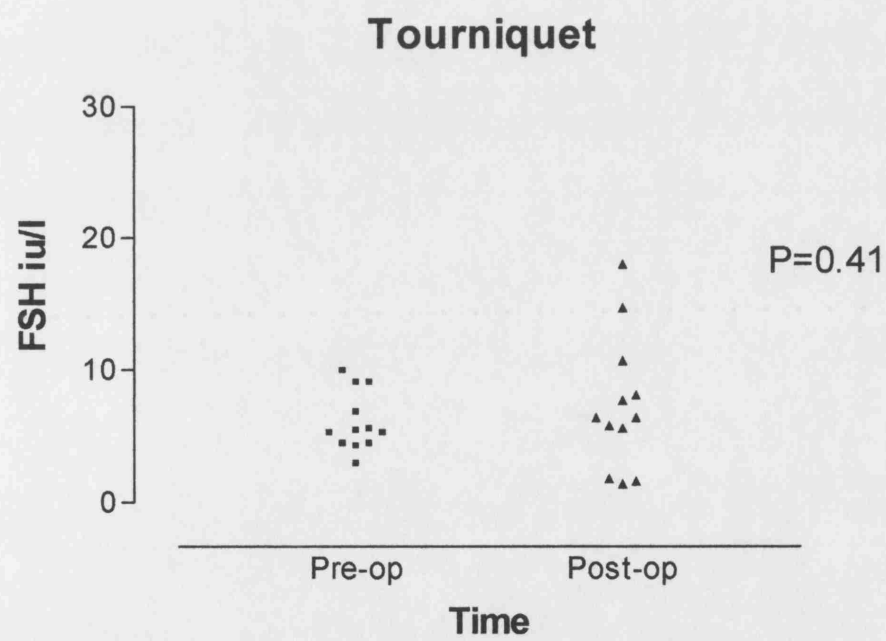
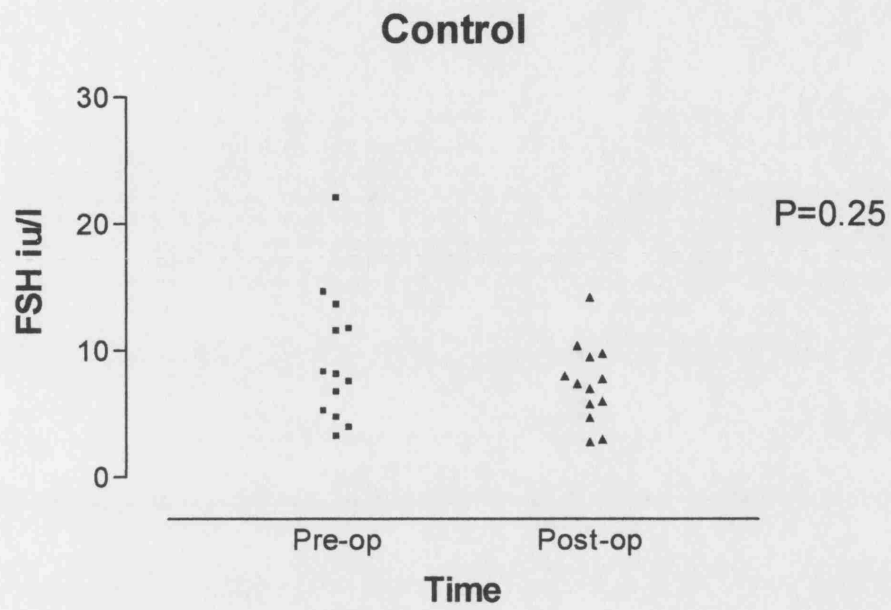
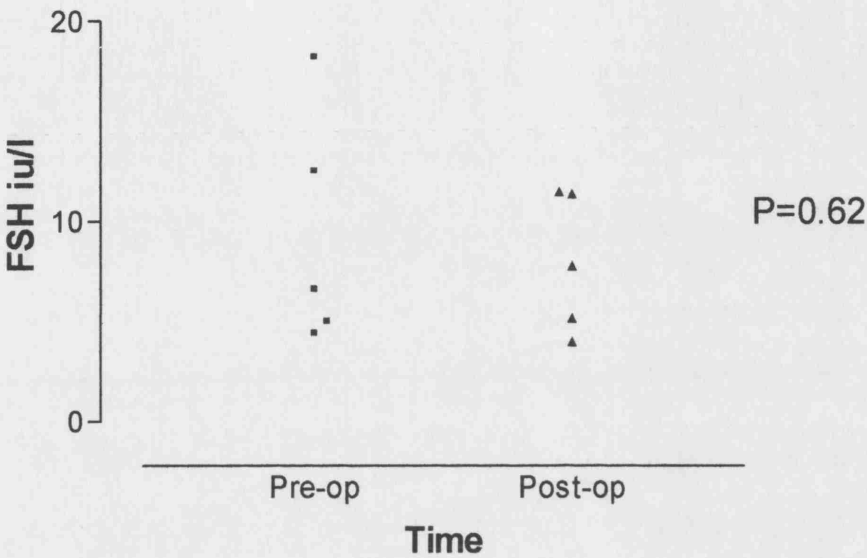


figure 23. Changes in serum FSH at Laparoscopic myomectomy with tourniquets



Chapter Eight: The effect of open myomectomy on menstrual blood loss

Introduction

One in 20 women aged 30-49 years consult their general practitioner each year with heavy periods (approximately 1.5 million women in England and Wales) ¹²⁸ and although they are often successfully managed in the community significant numbers are referred to secondary care. In fact heavy menstrual bleeding accounts for one in eight referrals to a gynaecologist ¹²⁹. Once referred 60% of women will have undergone a hysterectomy, within five years of referral ¹³⁰. Whilst hysterectomy, is the definitive surgical "cure", it is not without morbidity and is not appropriate for women who wish to preserve their fertility. By contrast myomectomy, preserves fertility and in theory should improve menorrhagia. However good research in this area is lacking and currently clinicians and patients rely on subjective measurements⁴⁵, on which to base their decision to proceed to surgery. For the first time this study attempted to quantify the effect of open myomectomy on menstrual blood loss.

Patients and Methods

A randomised controlled trial to assess the effectiveness of triple tourniquets as a haemostatic technique to reduce blood loss at open myomectomy was carried out at the Royal Free and Whittington Hospitals, between January 2002 to July 2003. The main outcome measure was intra-operative blood loss, but we also recorded data on a number of important secondary outcome measures including the effect of open myomectomy on menstrual blood loss. The detailed methodology of the trial has already been described in Chapter four.

Women filled out a menstrual pictogram for two periods pre-operatively and again for two periods at four to six months post-operatively¹⁰⁰. The PBAC score corresponded to blood loss in millilitres and menorrhagia was defined as a score of >80. All women were advised to use Tampax tampons and Kotex pads (as the pictograms had only been validated with these brands). A copy of the menstrual pictogram and score sheet can be found in appendix 2.

Statistics

Data was analysed with independent sampled t test, paired t test using SPSS® 11 software (SPSS Software, Chicago, Illinois, USA). We assumed significance at the 5% level ($p < 0.05$) and all tests were two sided.

Results

As already described, twenty-eight patients were recruited from a cohort of 171 patients referred to hospital for management of symptomatic uterine fibroids. They were randomization into two groups and both had similar baseline characteristics, including uterine size (Table 2). Twenty five women completed the menstrual pictograms, the remaining three, two from the control group and one from the tourniquet group, failed to complete the follow up questionnaire despite postal reminders.

Nineteen women had menorrhagia pre-operatively and three suffered from it post-operatively ($p < 0.0001$). There were significant reductions in menstrual

blood loss for both groups, but no significant differences between groups ($p=0.125$ [CI -5 to 40]). Total group scores were calculated for the cohort as a whole, comparing their post-operative scores with their pre-operative scores. For the group as a whole, menstrual blood loss reduced significantly following open myomectomy (Figure 24), with mean pre operative and post operative scores of 214 (SD 178) and 40 (SD 28) respectively, and the difference between the means was 172 ($p<0.0001$ [95% CI 98 to 249]).

Discussion

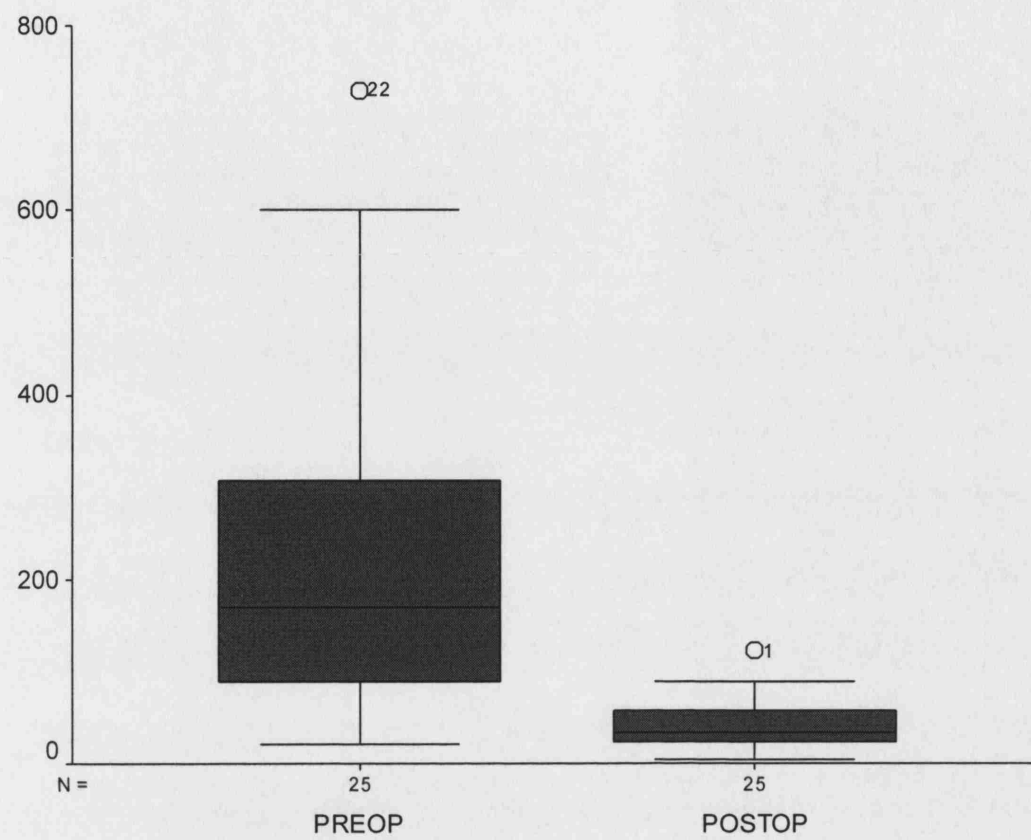
Pictorial charts were first introduced as an accurate and yet simple objective measure of menstrual blood loss ¹³¹. They provided clinicians and patients with a practical and convenient alternative to the time consuming alkaline haematin method ¹³². These early charts were reported to have a sensitivity of 86% and a specificity of 81% in diagnosing menorrhagia (defined as menstrual blood loss $\geq 80\text{ml}$ for the whole period). However, in recent years the accuracy of these charts has been questioned ¹³³. In response to the shortcomings of the original pictograms, they have since been refined and revalidated to reflect the differing levels of absorbency of blood on sanitary towels and tampons¹⁰⁰. It was these new and improved pictograms that we used to evaluate open myomectomy, as a treatment for menorrhagia.

The association with fibroids and heavy periods has long been reported ³, but the actual underlying pathophysiological is still not completely understood. There are several mechanisms that might explain their association with abnormal bleeding. Firstly, fibroids tend to increase the endometrial surface,

therefore increasing the volume of endometrium shed each month. Secondly, they are associated with angiogenesis and abnormal vessel characteristics ⁴¹. Finally it is possible that they interfere with normal uterine contractility at the time of menstruation. For all that they have been reported to be associated with abnormal bleeding³, data on the effectiveness of myomectomy is limited. Only vaginal myomectomy ¹³⁴and hysteroscopic myomectomy have been shown to reduce menstrual blood loss ^{135;136}. Objective evidence that open myomectomy improves menstrual blood loss is lacking. By contrast investigators evaluating uterine artery embolisation (UAE) have more recently shown a reduction in menorrhagia, using a five point scale¹³⁷.

To our knowledge, this is the first report showing an objective reduction in menstrual blood loss following the removal of fibroids at laparotomy. Although our prospective series is small we believe that it provides the best evidence to date that open myomectomy relieves menorrhagia.

figure 24. Mean menstrual blood loss scores pre and post myomectomy



- O²² AND O¹ are outliers

Chapter Nine: Psycho-social and quality of life data after open myomectomy

Introduction

Symptomatic fibroids can have a significant negative effect on a woman's psycho-social and psycho-sexual health. Heavy bleeding from fibroids can be socially embarrassing, restrict social activities and impair sexual arousal and performance. Infertility is well recognised as having negative psycho-emotional consequences ^{138;139} and pain and pelvic pressure symptoms can make life miserable for some women. Fibroids not only effect a woman's quality of life¹⁴⁰, but they can also have an adverse effect her economic health and that of her employer. Heavy periods are a well recognised cause of sick leave from work and have been estimated at an annual cost of \$1692 per woman ¹⁴¹.

Whilst surgery remains the mainstay of treatment, robust outcome data to suggest it improves quality of life is lacking ⁴⁵. Our study aims to provide clinicians and patients with good quality evidence on which to make informed decisions.

Patients and methods

From January 2002 to July 2003, patients seen in the Fibroid Clinic and Gynaecology Clinic at the Royal Free Hospital, and Gynaecology Clinic at the Whittington Hospital were assessed for entry into a randomised controlled trial, evaluating the use of triple tourniquets as a haemostatic technique to reduce blood loss at open myomectomy (see Chapter Four). The main outcome measure was intra-operative blood loss however we were also

interested in assessing the effect of myomectomy on quality of life. It is this data that is presented here.

As already described, twenty-eight patients were recruited from a cohort of 171 patients referred to hospital for management of symptomatic uterine fibroids. They were randomized into two groups and both had similar baseline characteristics, including uterine size (Table 2).

Quality of life was assessed by the Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QOL)¹⁰¹. This is a new questionnaire designed specifically to assess symptom severity and symptom impact on health related quality of life for women with fibroids. It consists of 72 items, 18 relating to symptoms and 54 relating quality of life. The symptom questions assess the frequency and severity of fibroid symptoms whilst the areas assessed by the quality of life questions are, fatigue, sleep, self-image, mood disturbance/psychological distress, fear of embarrassment, interference with daily activities, relationships with family and friends, and sexual functioning. Patients are presented with five response options ranging from “none of the time” to “all of the time” for symptom frequency and quality of life questions and “not at all” to “a very great deal” for the symptom severity questions. A copy of the questionnaire can be found in Appendix 2.

All 28 patients were given a questionnaire in the hospital outpatient clinic and asked to complete and return it, prior to their operation. Post-operatively at the six-month clinic check they were again asked to complete a questionnaire.

Statistics

Data was analysed with the independent sampled t test and the paired t test using SPSS® 11 software (SPSS Software, Chicago, Illinois, USA). We assumed significance at the 5% level ($p < 0.05$).

Results

Twenty-six women completed both pre-operative and post-operative UFS-QOL questionnaires. The remaining two, one from each group failed to complete the follow up questionnaire despite postal reminders.

There were significant improvements in symptom control for both groups, but no significant differences between groups based on any of the eight subscales within the UFS-QOL (Table 7). Total group scores were calculated for the cohort as a whole, comparing their post-operative scores with their pre-operative scores. Seven out of the eight measures were significantly improved (Table 8).

For the group as a whole, the symptom severity scale, a measure of menorrhagia, reduced significantly post open myomectomy figure 25 ($p < 0.001$ [CI 18-35]) and all subscales within the health related quality of life scale, improved significantly (concern $p < 0.001$ [CI 17-47], activities $p = 0.001$ [CI 10-33], energy/mood $p < 0.001$ [12-32], control $p < 0.001$ [CI 12-32], self consciousness $p < 0.003$ [CI 8-35]), except for sexual function which did not significantly improve ($p = 0.114$ [CI -2-22]). An overall score was given by the HRQL total, where a *higher* score was indicative of a better outcome. This again was significantly improved HRQL total $p < 0.001$ [CI (-13)-(-34)].

Discussion

Health related quality of life questionnaires are not new ¹⁴². However they tend to be generic and this “one size fits all approach” limits their sensitivity when measuring outcomes unique to a particular condition. Despite this they have often been used in surgical trials to measure symptom alleviation ^{143;144}.

Questionnaires specific to gynaecological symptoms have been developed such as the Menorrhagia Questionnaire ¹⁴⁵ but these do not assess the non-bleeding symptoms of fibroids, such as pelvic pressure, urinary frequency and pelvic discomfort. Nor do they assess the impact of symptoms on quality of life. Only one fibroid specific questionnaire has been developed, it was designed to assess the effect of uterine artery embolization on fibroid symptoms ¹⁴⁶. However this questionnaire did not include a patient perspective and was based on a generic health status questionnaire. The new UFS-QOL questionnaire, by contrast is specific to leiomyomata and incorporates a patients perspective, which therefore makes it, a much more powerful tool when assessing interventions specific to fibroids. It has been rigorously evaluated and validated using a number of instruments, including the Short-Form 36 Health survey, the Menorrhagia Questionnaire and the Revicki-Wu sexual function scale ¹⁰¹.

This small but meticulous study shows that at six months post myomectomy women report significantly improved menstrual loss and an improvement in all but one of the other quality of life measures (sexual function). Although there was a reduction in post-operative scores for sexual function, this was not significant. However, it may be that a six-month follow up period was too short.

Researchers evaluating the effect of hysterectomy on sexual function, only reported significant improvements at twelve months ¹⁴⁷.

Although not powered to detect a difference in symptom outcome using the UFS-QOL we were nonetheless interested to see if our absorbable cervical tourniquet, improved symptom relief more than a standard myomectomy. The theory being that there would be less post-operative bleeding, therefore less adhesion development and perhaps therefore an increase in quality of life scores. However although there appeared to be a trend towards lower post-procedure scores compared to pre-procedure scores, crucially the differences between the two groups were not significant.

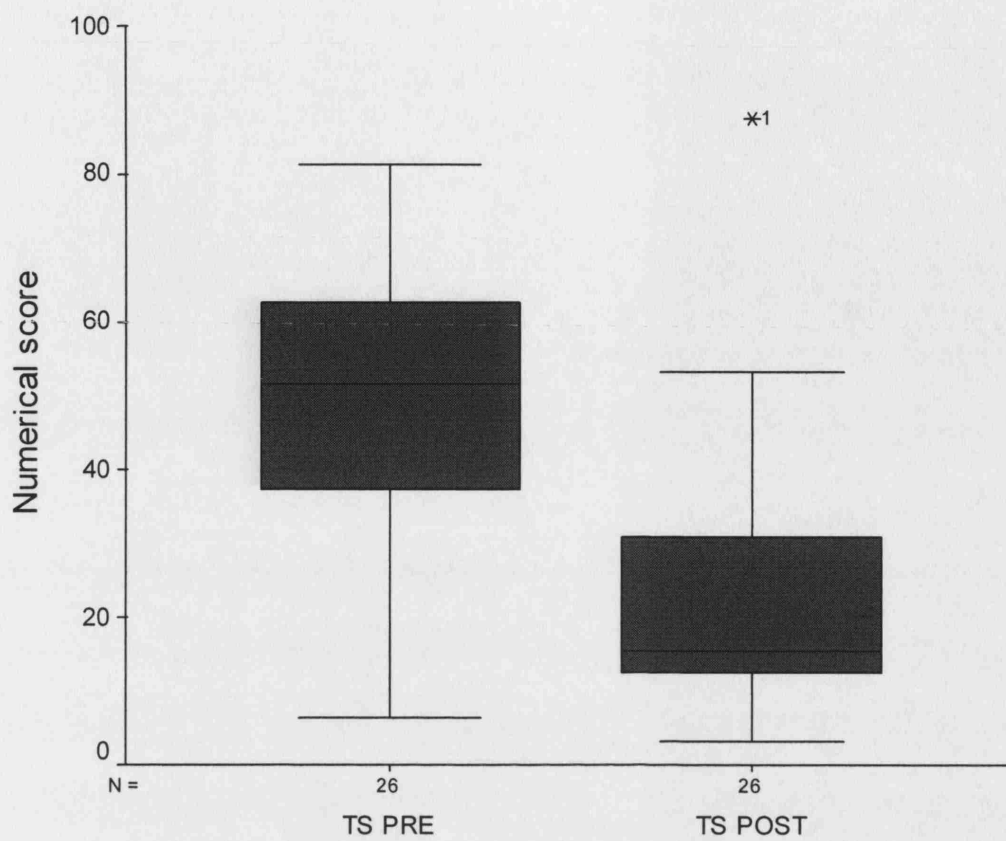
Table 7. Mean scores of UFS-QOL

	Control Group (n=13)			Tourniquet Group (n=13)			Differences between means
	Pre-op scores	Post-op scores	p	Pre-op scores	Post-op scores	p	p
Symptom severity (menorrhagia)	50	26	0.001	49	18	<0.001	0.75
Concern	46	20	0.013	55	15	0.005	0.67
Activities	39	23	0.05	45	16	0.007	0.4
Energy/mood	40	20	0.016	46	20	0.006	0.97
Control	42	23	0.015	42	15	0.004	0.37
Self-conscious	45	30	0.13	50	21	0.009	0.42
Sexual function	30	24	0.59	35	21	0.065	0.73
HRQL Total	58	76	0.022	55	79	0.002	0.53

Table 8 Total group mean scores of UFS-QOL

	Group	Scores	(n=26)	
	Pre-op scores	Post-op scores	p	CI
Symptom severity (menorrhagia)	50	22	<0.001	18-35
Concern	20	15	<0.001	17-47
Activities	42	20	0.001	10-33
Energy/mood	43	20	<0.001	12-32
Control	43	20	<0.001	12-32
Self-conscious	48	26	0.003	8-35
Sexual function	32	22	0.114	(-2)-22
HRQL Total	55	79	<0.001	(-34)-(-13)

figure 25. Mean group scores for menorrhagia pre and post myomectomy



Chapter Ten: Summary

1) The majority of women with symptomatic fibroids continue to be managed surgically in the UK. Open and hysteroscopic myomectomy are frequently utilised in contrast to laparoscopic myomectomy. The use of pre-operative GnRHa appears widespread whereas intra-operative techniques for reducing blood loss at open and at laparoscopic myomectomy appear more varied. The reported rate of blood transfusion appears lower than that reported in the literature. Whilst the majority of respondents now have access to UAE, the numbers of women referred for the procedure remains low.

2) Triple tourniquets are effective in reducing the blood loss and the morbidity of open myomectomy. The use of an absorbable cervical tourniquet left in situ post-operatively, may reduce peri-operative bleeding.

3) The use of triple tourniquets at laparoscopic myomectomy is feasible and in principle should reduce operative blood loss. In addition, the use of an absorbable uterine tourniquet may also reduce post-operative bleeding.

4) Ultrasound Doppler evaluation of the absorbable cervical tourniquet suggests that such a tourniquet has no long-term harmful effects on uterine reperfusion.

5) The use of ovarian tourniquets does not appear to be harmful to ovarian function.

6) Given, the triple tourniquets advantages over alternative hemostatic techniques I would recommend their routine use at open myomectomy.

7) In 1997, the costs of surgical management of fibroids in the USA, exceeded \$2 billion and yet good evidence supporting this intervention was lacking.

Although our prospective series is small it provides the best evidence to date that open myomectomy relieves menorrhagia and improves quality of life.

Chapter Eleven: Future research

The pathophysiology of leiomyomas is slowly being unravelled. Advances in our understanding of the underlying molecular biology and genetics of fibroid development is opening up new therapeutic avenues which are even now being explored in vitro. However, there remains a long way to go before new medical treatment options are available to clinicians and patients.

By contrast, myomectomy is well established and has been with us for nearly a hundred years. Medicine has changed enormously in that time, including the way we practise and the way new treatments are evaluated. Evidence based practice is part of that change and randomised controlled trials are the gold standard within evidence based medicine. However performing randomised controlled trials in surgery is difficult and I believe far more difficult than organising similar trials for a new drug. This is because it is often unethical to have a control group, patients may decline randomisation and instead may request a particular operation. Also whilst quality control measures can ensure drug uniformity in a medical trial, such quality control measures are much harder to incorporate into surgical trials where there are many more variables such as different surgeons, different centres, different post operative teams, all of which can effect the outcome. Such difficulties have called some authors to question the place of surgical RCTs and instead have called for a return to personal audit ¹⁴⁸. Despite all of these difficulties though randomised controlled trials, remain the gold standard, not least because patients increasingly want to know the benefits and risks of surgery, in order to make an informed choice about treatment options.

The rationale for this thesis reflects this change and the results re-evaluate myomectomy in line with current thinking and practise. However this is just a small step in that process. For the future, the triple tourniquets need to be evaluated against GnRHa (the commonest haemostatic technique employed in the UK) and an appropriately powered study needs to be conducted to see if an absorbable cervical tourniquet left in situ post-operatively reduces post-operative blood loss. Having determined that the use of triple tourniquets at laparoscopic myomectomy is feasible, their effectiveness needs to be evaluated in a randomised controlled trial. Also unlike at open myomectomy, at laparoscopic myomectomy (where there is generally a smaller uterus and therefore less blood flow) it might be possible to use only a single cervical absorbable tourniquet. This would in theory reduce the operating time and avoid temporary occlusion of the ovarian vessels. These outcomes and its effect on intra-operative blood loss should be evaluated in a single versus triple tourniquet trial.

The results on symptom relief and improvement are new and exciting, but they remain only short-term data at the moment. The women from the open myomectomy study should be followed up in the medium to longer term, to determine the outcome of myomectomy on menstrual blood loss and quality of life.

It is also important to determine the effect of the absorbable tourniquet on fibroid recurrence. Standard techniques have reported a 50 % five year recurrence rate ¹⁴⁹, whereas recent data on uterine artery ligation at

myomectomy has suggested this leads to no recurrences at two years ¹¹¹.

What effect will our novel cervical tourniquet have?

I believe our work has significantly contributed to our knowledge base on the technique of myomectomy and its clinical effectiveness. This is of real benefit to patients and to the gynaecological community. However much research remains to be done before patients opting for myomectomy can be said to be “fully informed”.

Appendix 1

Reference List

1. Townsend DE, Sparkes RS, Baluda MC, McClelland G. Unicellular histogenesis of uterine leiomyomas as determined by electrophoresis by glucose-6-phosphate dehydrogenase. *Am.J.Obstet.Gynecol.* 1970;107:1168-73.
2. Benda JA. Pathology of smooth muscle tumors of the uterine corpus. *Clin.Obstet.Gynecol.* 2001;44:350-63.
3. Buttram VC, Jr. Uterine leiomyomata--aetiology, symptomatology and management. *Prog.Clin.Biol.Res.* 1986;225:275-96.
4. Cramer SF, Patel A. The frequency of uterine leiomyomas. *Am.J.Clin.Pathol.* 1990; 94:435-8.
5. Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA *et al.* Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. *Obstet.Gynecol.* 1997; 90:967-73.
6. Day BD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am.J.Obstet.Gynecol.* 2003; 188:100-7.
7. Borgfeldt C, Andolf E. Transvaginal ultrasonographic findings in the uterus and the endometrium: low prevalence of leiomyoma in a random sample of women age 25-40 years. *Acta Obstet.Gynecol.Scand.* 2000; 79:202-7.
8. Ross RK, Pike MC, Vessey MP, Bull D, Yeates D, Casagrande JT. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *Br.Med.J. (Clin.Res.Ed)* 1986; 293:359-62.
9. Lumbiganon P, Ruggao S, Phandhu-fung S, Laopaiboon M, Vudhikamraksa N, Werawatakul Y. Protective effect of depot-medroxyprogesterone acetate on surgically treated uterine leiomyomas: a multicentre case--control study. *Br.J.Obstet.Gynaecol.* 1996; 103:909-14.
10. Parazzini F, Negri E, La Vecchia C, Fedele L, Rabaiotti M, Luchini L. Oral contraceptive use and risk of uterine fibroids. *Obstet.Gynecol.* 1992; 79:430-3.
11. Ramacharan S, Pelligrin FA, Ray R, Hsu J. The Walnut Creek contraceptive drug study. A prospective study of the side effects of oral contraceptives. *Center popul Res Monogr* 1981;3:69-74.
12. Marshall LM, Spiegelman D, Goldman MB, Manson JE, Colditz GA, Barbieri RL *et al.* A prospective study of reproductive factors and oral

contraceptive use in relation to the risk of uterine leiomyomata.
Fertil.Steril. 1998; 70:432-9.

13. Chiaffarino F, Parazzini F, La Vecchia C, Marsico S, Surace M, Ricci E. Use of oral contraceptives and uterine fibroids: results from a case-control study. *Br.J.Obstet.Gynaecol.* 1999; 106:857-60.
14. Marshall LM, Spiegelman D, Manson JE, Goldman MB, Barbieri RL, Stampfer MJ *et al.* Risk of uterine leiomyomata among premenopausal women in relation to body size and cigarette smoking. *Epidemiology* 1998; 9:511-7.
15. Parazzini F, Negri E, La Vecchia C, Rabaiotti M, Luchini L, Villa A *et al.* Uterine myomas and smoking. Results from an Italian study. *J.Reprod.Med.* 1996; 41:316-20.
16. Chiaffarino F, Parazzini F, La Vecchia C, Chatenoud L, Di Cintio E, Marsico S. Diet and uterine myomas. *Obstet.Gynecol.* 1999;94:395-8.
17. Clement PB. The pathology of uterine smooth muscle tumors and mixed endometrial stromal-smooth muscle tumors: a selective review with emphasis on recent advances. *Int.J.Gynecol.Pathol.* 2000; 19:39-55.
18. Major FJ, Blessing JA, Silverberg SG, Morrow CP, Creasman WT, Currie JL *et al.* Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. *Cancer* 1993; 71:1702-9.
19. Taylor HB, Norris HJ. Mesenchymal tumors of the uterus. IV. Diagnosis and prognosis of leiomyosarcomas. *Arch.Pathol.* 1966; 82:40-4.
20. Gross KL, Morton CC. Genetics and the development of fibroids. *Clin.Obstet.Gynecol.* 2001; 44:335-49.
21. Rein MS, Friedman AJ, Barbieri RL, Pavelka K, Fletcher JA, Morton CC. Cytogenetic abnormalities in uterine leiomyomata. *Obstet.Gynecol.* 1991; 77:923-6.
22. Rein MS, Powell WL, Walters FC. Cytogenetic abnormalities in uterine myomas are associated with myoma size. *Mol Hum Reprod* 1998; 4:83-6.
23. Meloni AM, Surti U, Contento AM, Davare J, Sandberg AA. Uterine leiomyomas: cytogenetic and histologic profile. *Obstet.Gynecol.* 1992; 80:209-17.
24. Hu J, Surti U. Subgroups of uterine leiomyomas based on cytogenetic analysis. *Hum.Pathol.* 1991; 22:1009-16.
25. Turc-Carel C, Dal Cin P, Rao U, Karakousis C, Sandberg AA. Cytogenetic studies of adipose tissue tumors. I. A benign lipoma with

reciprocal translocation t(3;12)(q28;q14). *Cancer Genet.Cytogenet.* 1986; 23:283-9.

26. Bullerdiek J, Bartnitzke S, Weinberg M, Chilla R, Haubrich J, Schloot W. Rearrangements of chromosome region 12q13----q15 in pleomorphic adenomas of the human salivary gland (PSA). *Cytogenet.Cell Genet.* 1987; 45:187-90.
27. John S, Reeves RB, Lin JX, Child R, Leiden JM, Thompson CB *et al.* Regulation of cell-type-specific interleukin-2 receptor alpha-chain gene expression: potential role of physical interactions between Elf-1, HMG-I(Y), and NF-kappa B family proteins. *Mol Cell Biol.* 1995; 15:1786-96.
28. Pellacani A, Wiesel P, Razavi S, Vasilj V, Feinberg MW, Chin MT *et al.* Down-regulation of high mobility group-I(Y) protein contributes to the inhibition of nitric-oxide synthase 2 by transforming growth factor-beta1. *J.Biol.Chem.* 2001; 276:1653-9.
29. Treloar SA, Martin NG, Dennerstein L, Raphael B, Heath AC. Pathways to hysterectomy: insights from longitudinal twin research. *Am.J.Obstet.Gynecol.* 1992; 167:82-8.
30. Vikhlyaeva EM, Khodzhaeva ZS, Fantschenko ND. Familial predisposition to uterine leiomyomas. *Int.J.Gynaecol.Obstet.* 1995; 51:127-31.
31. Reed WB, Walker R, Horowitz R. Cutaneous leiomyomata with uterine leiomyomata. *Acta Derm.Venereol.* 1973; 53:409-16.
32. Stewart EA, Friedman AJ. Steroidal treatment of leiomyomas: preoperative and long-term medical therapy. *Semin Reprod Endocrinol* 1992; 10:344-57.
33. Brandon DD, Erickson TE, Keenan EJ, Strawn EY, Novy MJ, Burry KA *et al.* Estrogen receptor gene expression in human uterine leiomyomata. *J.Clin.Endocrinol Metab* 1995; 80:1876-81.
34. Sumitani H, Shozu M, Segawa T, Murakami K, Yang HJ, Shimada K *et al.* In situ estrogen synthesized by aromatase P450 in uterine leiomyoma cells promotes cell growth probably via an autocrine/intracrine mechanism. *Endocrinology* 2000; 141:3852-61.
35. Matsuo H, Maruo T, Samoto T. Increased expression of Bcl-2 protein in human uterine leiomyoma and its up-regulation by progesterone. *J.Clin.Endocrinol Metab* 1997; 82:293-9.
36. Africa A, Sozen I. Transforming growth factor-beta3 is expressed at high levels in leiomyoma where it stimulates fibronectin expression and cell proliferation. *Fertil.Steril.* 2000; 73:1006-11.
37. Nowak RA. Identification of new therapies for leiomyomas: what in vitro studies can tell us. *Clin.Obstet.Gynecol.* 2001; 44:327-34.

38. Boehm KD, Daimon M, Gorodeski IG, Sheean LA, Utian WH, Ilan J. Expression of the insulin-like and platelet-derived growth factor genes in human uterine tissues. *Mol Reprod Dev.* 1990; 27:93-101.
39. Strawn EY, Jr., Novy MJ, Burry KA, Bethea CL. Insulin-like growth factor I promotes leiomyoma cell growth in vitro. *Am.J.Obstet.Gynecol.* 1995; 172:1837-43.
40. Stovall DW. Clinical symptomatology of uterine leiomyomas. *Clin.Obstet.Gynecol.* 2001; 44:364-71.
41. Stewart EA, Nowak RA. Leiomyoma-related bleeding: a classic hypothesis updated for the molecular era. *Hum Reprod Update.* 1996; 2:295-306.
42. Farhi J, Ashkenazi J, Feldberg D, Dicker D, Orvieto R, Ben Rafael Z. Effect of uterine leiomyomata on the results of in-vitro fertilization treatment. *Hum Reprod* 1995; 10:2576-8.
43. Hart R, Khalaf Y, Yeong CT, Seed P, Taylor A, Braude P. A prospective controlled study of the effect of intramural uterine fibroids on the outcome of assisted conception. *Hum Reprod* 2001; 16:2411-7.
44. Lippman SA, Warner M, Samuels S, Olive D, Vercellini P, Eskenazi B. Uterine fibroids and gynecologic pain symptoms in a population-based study. *Fertil.Steril.* 2003; 80:1488-94.
45. Myers ER, Barber MW, Couchman GM, Datta S, Gray RN, and Gustilo-Ashby T et al. Management of uterine fibroids. Evidence report/technology assessment. Rockville, MD: Agency for Healthcare Research Quality. 2001.
Ref Type: Report
46. Friedman AJ, Thomas PP. Does low-dose combination oral contraceptive use affect uterine size or menstrual flow in premenopausal women with leiomyomas? *Obstet.Gynecol.* 1995;85:631-5.
47. Ylikorkala O, Pekonen F. Naproxen reduces idiopathic but not fibromyoma-induced menorrhagia. *Obstet.Gynecol.* 1986; 68:10-2.
48. Lethaby A, Vollenhoven B, Sowter M. Efficacy of pre-operative gonadotrophin hormone releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy: a systematic review. *BJOG.* 2002;109:1097-108.
49. Friedman AJ, Barbieri RL, Doubilet PM, Fine C, Schiff I. A randomized, double-blind trial of a gonadotropin releasing-hormone agonist (leuprolide) with or without medroxyprogesterone acetate in the treatment of leiomyomata uteri. *Fertil.Steril.* 1988; 49:404-9.

50. Friedman AJ, Daly M, Juneau-Norcross M, Gleason R, Rein MS, LeBoff M. Long-term medical therapy for leiomyomata uteri: a prospective, randomized study of leuprolide acetate depot plus either oestrogen-progestin or progestin 'add-back' for 2 years. *Hum Reprod* 1994; 9:1618-25.
51. Scialli AR, Levi AJ. Intermittent leuprolide acetate for the nonsurgical management of women with leiomyomata uteri. *Fertil.Steril.* 2000; 74:540-6.
52. Eisinger SH, Meldrum S, Fiscella K, le Roux HD, Guzick DS. Low-dose mifepristone for uterine leiomyomata. *Obstet.Gynecol.* 2003;101:243-50.
53. Ravina JH, Merland JJ, Herbreteau D, Houdart E, Bouret JM, Madelenat P. [Preoperative embolization of uterine fibroma. Preliminary results (10 cases)]. *Presse Med* 1994; 23:1540.
54. Ravina JH, Herbreteau D, Ciraru-Vigneron N, Bouret JM, Houdart E, Aymard A *et al.* Arterial embolisation to treat uterine myomata. *Lancet* 1995; 346:671-2.
55. Walker WJ, Pelage JP. Uterine artery embolisation for symptomatic fibroids: clinical results in 400 women with imaging follow up. *BJOG.* 2002; 109:1262-72.
56. Vashisht A, Studd J, Carey A, Burn P. Fatal septicaemia after fibroid embolisation. *Lancet* 1999; 354:307-8.
57. de Blok S, de Vries C, Prinssen HM, Blaauwgeers HL, Jorna-Meijer LB. Fatal sepsis after uterine artery embolization with microspheres. *J Vasc.Interv.Radiol.* 2003; 14:779-83.
58. Lanocita R, Patelli G, Spreafico C, and Di Tolla G. A fatal complication of percutaneous transcatheter embolization for the treatment of fibroids. 2004. Second International Symposium on Embolization of Uterine Myomata/Society for Minimally Invasive Therapy 11th International Conference, Boston. 1999.
Ref Type: Conference Proceeding
59. Braude P, Reidy J, Nott V, Taylor A, Forman R. Embolization of uterine leiomyomata: current concepts in management. *Hum Reprod Update.* 2000;6:603-8.
60. Amato P, Roberts AC. Transient ovarian failure: a complication of uterine artery embolization. *Fertil.Steril.* 2001; 75:438-9.
61. Chrisman HB, Saker MB, Ryu RK, Nemcek AA, Jr., Gerbie MV, Milad MP *et al.* The impact of uterine fibroid embolization on resumption of menses and ovarian function. *J Vasc.Interv.Radiol.* 2000; 11:699-703.

62. Ryu RK, Chrisman HB, Omary RA, Miljkovic S, Nemcek AA, Jr., Saker MB *et al.* The vascular impact of uterine artery embolization: prospective sonographic assessment of ovarian arterial circulation. *J Vasc.Interv.Radiol.* 2001;12:1071-4.
63. Molley D. Uterine artery embolisation (UAE) its current status in Australia. *Scope, Newsletter Australian Gynaecological Society* 2004; 24:10-2.
64. The Royal College of Obstetricians & Gynaecologists. Clinical Recommendations on the use of Fibroid Embolisation in the management of uterine fibroids. Report of a joint working party. 2001. RCOG Press.
Ref Type: Report
65. Nisolle M, Smets M, Malvaux V, Anaf V, Donnez J. Laparoscopic myolysis with the Nd:YAG laser. *J Gynecol.Surg.* 1993;9:95-9.
66. Law P, Gedroyc WM, Regan L. Magnetic-resonance-guided percutaneous laser ablation of uterine fibroids. *Lancet* 1999;354:2049-50.
67. Hindley JT, Law PA, Hickey M, Smith SC, Lamping DL, Gedroyc WM *et al.* Clinical outcomes following percutaneous magnetic resonance image guided laser ablation of symptomatic uterine fibroids. *Hum Reprod* 2002;17:2737-41.
68. Bonney V. The technique and results of myomectomy. *Lancet* 1931;220:171-7.
69. Atlee WL. Case of a successful extirpation of a fibroid tumour of the peritoneal surface of the uterus by the large peritoneal section. *Am J Med Sci* 1845;9:309-35.
70. Neuwirth RS. A new technique for and additional experience with hysteroscopic resection of submucous fibroids. *Am J Obstet.Gynecol.* 1978;131:91-4.
71. Semm K. New methods of pelviscopy (gynecologic laparoscopy) for myomectomy, ovariectomy, tubectomy and adnectomy. *Endoscopy* 1979;11:85-93.
72. Dubuisson JB, Chapron C, Fauconnier A. Laparoscopic myomectomy. In Sutton C, Diamond M, eds. pp 272-9. *Endoscopic Surgery for Gynaecologists*: W B Saunders, 1998.
73. Hospital Episode Statistics.
http://www.doh.gov.uk/hes/free_data/index.html 2001.
74. Fletcher H, Frederick J, Hardie M, Simeon D. A randomized comparison of vasopressin and tourniquet as hemostatic agents during myomectomy. *Obstet.Gynecol.* 1996;87:1014-8.

75. Berkeley AS, DeCherney AH, Polan ML. Abdominal myomectomy and subsequent fertility. *Surg.Gynecol.Obstet.* 1983;156:319-22.
76. Ginsburg ES, Benson CB, Garfield JM, Gleason RE, Friedman AJ. The effect of operative technique and uterine size on blood loss during myomectomy: a prospective randomized study. *Fertil.Steril.* 1993;60:956-62.
77. Gehlbach DL, Sousa RC, Carpenter SE, Rock JA. Abdominal myomectomy in the treatment of infertility. *Int.J.Gynaecol.Obstet.* 1993;40:45-50.
78. Rubin IC. The pericervical broad ligament tourniquet for preventive hemostasis in myomectomy. *Obstet.Gynecol.* 1953;1:668-71.
79. Sapmaz E, Celik H, Altungul A. Bilateral ascending uterine artery ligation vs. tourniquet use for hemostasis in cesarean myomectomy. A comparison. *J Reprod Med* 2003;48:950-4.
80. Sapmaz E, Celik H. Comparison of the effects of the ligation of ascending branches of bilateral arteria uterina with tourniquet method on the intra-operative and post-operative hemorrhage in abdominal myomectomy cases. *Eur.J Obstet.Gynecol.Reprod Biol.* 2003;111:74-7.
81. Schifano MJ, Hoshaw NJ, Boushka WM, Alvero RJ. Uterine artery embolization in a hemorrhaging postoperative myomectomy patient. *Obstet.Gynecol.Surv.* 1999;54:1-3.
82. Dubuisson JB, Chapron C. Laparoscopic myomectomy and myolysis. *Baillieres Clin.Obstet.Gynaecol.* 1995;9:717-28.
83. Dubuisson JB. Management of leiomyomata. *Hum.Reprod.Update.* 2000;6:587.
84. Mais V, Ajossa S, Guerriero S, Mascia M, Solla E, Melis GB. Laparoscopic versus abdominal myomectomy: a prospective, randomized trial to evaluate benefits in early outcome. *Am.J.Obstet.Gynecol.* 1996;174:654-8.
85. Seracchioli R, Rossi S, Govoni F, Rossi E, Venturoli S, Bulletti C *et al.* Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal myomectomy. *Hum.Reprod.* 2000;15:2663-8.
86. Goldfarb HA. Laparoscopic coagulation of myoma (myolysis). *Obstet.Gynecol.Clin.North Am* 1995;22:807-19.
87. Liu WM, Ng HT, Wu YC, Yen YK, Yuan CC. Laparoscopic bipolar coagulation of uterine vessels: a new method for treating symptomatic fibroids. *Fertil.Steril.* 2001;75:417-22.

88. Pelosi MA, Pelosi MA, III, Eim J. Hand-assisted laparoscopy for megamyomectomy. A case report. *J Reprod Med* 2000;45:519-25.
89. Tulandi T, Beique F, Kimia M. Pulmonary edema: a complication of local injection of vasopressin at laparoscopy. *Fertil.Steril.* 1996;66:478-80.
90. Ostrzenski A. A new laparoscopic myomectomy technique for intramural fibroids penetrating the uterine cavity. *Eur.J.Obstet.Gynecol.Reprod.Biol.* 1997;74:189-93.
91. Goldfarb HA. Myoma coagulation (myolysis). *Obstet.Gynecol.Clin.North Am.* 2000;27:421-30.
92. Hindley JT, Gedroyc WM, Regan L. Interstitial laser coagulation for uterine myomas. *Am.J.Obstet.Gynecol.* 2003;188:859.
93. Lethaby A, Vollenhoven B. Fibroids (uterine myomatosis, leiomyomas). *Clin.Evid.* 2002;1666-78.
94. LaMorte AJ, Lalwani S, Diamond MP. Morbidity associated with abdominal myomectomy. *Obstet.Gynecol.* 1993;82:897-900.
95. Togashi K, Ozasa H, Konishi I, Itoh H, Nishimura K, Fujisawa I *et al.* Enlarged uterus: differentiation between adenomyosis and leiomyoma with MR imaging. *Radiology* 1989;171:531-4.
96. Hricak H, Rubinstein LV, Gherman GM, Karstaedt N. MR imaging evaluation of endometrial carcinoma: results of an NCI cooperative study. *Radiology* 1991;179:829-32.
97. Dubuisson JB, Fauconnier A, Fourchette V, Babaki-Fard K, Coste J, Chapron C. Laparoscopic myomectomy: predicting the risk of conversion to an open procedure. *Hum.Reprod.* 2001;16:1726-31.
98. Taylor A, Magos A. Control of menorrhagia by endometrial resection. In Eric Bieber, Franklin Loffer, eds. *Hysteroscopy, Resectoscopy and Endometrial Ablation*, Parthenon Publishing, 2003.
99. Rubin IC. Uterine fibromyomas and sterility. *Clin.Obstet.Gynecol.* 1958;1:501-18.
100. Wyatt KM, Dimmock PW, Walker TJ, O'Brien PM. Determination of total menstrual blood loss. *Fertil.Steril.* 2001;76:125-31.
101. Spies JB, Coyne K, Guaou GN, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. *Obstet.Gynecol.* 2002;99:290-300.

102. Frederick J, Fletcher H, Simeon D, Mullings A, Hardie M. Intramyometrial vasopressin as a haemostatic agent during myomectomy. *Br.J.Obstet.Gynaecol.* 1994;101:435-7.
103. Friedman AJ, Rein MS, Harrison-Atlas D, Garfield JM, Doubilet PM. A randomized, placebo-controlled, double-blind study evaluating leuprolide acetate depot treatment before myomectomy. *Fertil.Steril.* 1989;52:728-33.
104. Thompson JD RJ. Leiomyomata uteri and myomectomy. In Rock JA TJe, ed. *Te Linde's Operative Gynaecology*, pp 731-70. Philadelphia: Lippincott-Raven Publishers, 1997.
105. Alexander W. *M.Press & Circular* 1898;66:349.
106. Lock FR. Multiple myomectomy. *Am.J.Obstet.Gynecol.* 1969;104:642-50.
107. Nezhat F, Admon D, Nezhat CH, Dicorpo JE, Nezhat C. Life-threatening hypotension after vasopressin injection during operative laparoscopy, followed by uneventful repeat laparoscopy. *J.Am.Assoc.Gynecol.Laparosc.* 1994;2:83-6.
108. Martin JD, Shenk LG. Intraoperative myocardial infarction after paracervical vasopressin infiltration. *Anesth.Analg.* 1994;79:1201-2.
109. Cantuaria GH, Angioli R, Frost L, Duncan R, Penalver MA. Comparison of bimanual examination with ultrasound examination before hysterectomy for uterine leiomyoma. *Obstet.Gynecol.* 1998;92:109-12.
110. Celik H, Sapmaz E. Use of a single preoperative dose of misoprostol is efficacious for patients who undergo abdominal myomectomy. *Fertil.Steril.* 2003;79:1207-10.
111. Liu WM, Tzeng CR, Yi-Jen C, Wang PH. Combining the uterine depletion procedure and myomectomy may be useful for treating symptomatic fibroids. *Fertil.Steril.* 2004;82:205-10.
112. Saad AG, Kaouk JH, Kaspar HG, Khauli RB. Leiomyoma of the urethra: report of 3 cases of a rare entity. *Int.J.Surg.Pathol.* 2003;11:123-6.
113. McLucas B, Perrella R, Goodwin S, Adler L, Dalrymple J. Role of uterine artery Doppler flow in fibroid embolization. *J.Ultrasound Med.* 2002;21:113-20.
114. Ochi H, Matsubara K, Kusanagi Y, Taniguchi H, Ito M. Significance of a diastolic notch in the uterine artery flow velocity waveform induced by uterine embolisation in the pregnant ewe. *Br.J.Obstet.Gynaecol.* 1998;105:1118-21.

115. Seiner P, Gaglioti P, Volpi E, Cau MA, Todros T. Ultrasound evaluation of uterine wound healing following laparoscopic myomectomy: preliminary results. *Hum Reprod* 1999;14:2460-3.
116. Donald I, MACVICAR J, Brown TG. Investigation of abdominal masses by pulsed ultrasound. *Lancet* 1958;1:1188-95.
117. Donnelly R, Hinwood D, London NJ. ABC of arterial and venous disease. Non-invasive methods of arterial and venous assessment. *BMJ* 2000;320:698-701.
118. Clark SL, Phelan JP, Yeh SY, Bruce SR, Paul RH. Hypogastric artery ligation for obstetric hemorrhage. *Obstet.Gynecol.* 1985;66:353-6.
119. Bonnar J. Massive obstetric haemorrhage. *Baillieres Best.Pract.Res Clin.Obstet.Gynaecol* 2000;14:1-18.
120. Bonney V. The technical minutiae of extended myomectomy and ovarian cystectomy. Cassell & Co. Ltd, 1946.
121. Aravantinos DJ. Keeping or removing the ovaries at the time of hysterectomy. *Eur.J Obstet.Gynecol.Reprod Biol.* 1988;28:140-6.
122. Machin D, Williams JD. The effect of hysterectomy on the age at ovarian failure. *Fertil.Steril.* 1988;49:378-80.
123. Siddle N, Sarrel P, Whitehead M. The effect of hysterectomy on the age at ovarian failure: identification of a subgroup of women with premature loss of ovarian function and literature review. *Fertil.Steril.* 1987;47:94-100.
124. Spies JB, Roth AR, Gonsalves SM, Murphy-Skrzyniarz KM. Ovarian function after uterine artery embolization for leiomyomata: assessment with use of serum follicle stimulating hormone assay. *J.Vasc.Interv.Radiol.* 2001;12:437-42.
125. DeLancey JO. A modified technique for hemostasis during myomectomy. *Surg.Gynecol.Obstet.* 1992;174:153-4.
126. Jeremias E, Bedaiwy MA, Gurunluoglu R, Biscotti CV, Siemionow M, Falcone T. Heterotopic autotransplantation of the ovary with microvascular anastomosis: a novel surgical technique. *Fertil.Steril.* 2002;77:1278-82.
127. Lutchman SK, Davies M, Chatterjee R. Fertility in female cancer survivors: pathophysiology, preservation and the role of ovarian reserve testing. *Hum Reprod Update.* 2005;11:69-89.
128. Garside R, Stein K, Wyatt K, Round A, Price A. The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling. *Health Technol.Assess.* 2004;8:iii, 1-iii155.

129. Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. *Cochrane.Database.Syst.Rev.* 2000;CD000249.
130. Coulter A, Bradlow J, Agass M, Martin-Bates C, Tulloch A. Outcomes of referrals to gynaecology outpatient clinics for menstrual problems: an audit of general practice records. *Br.J Obstet.Gynaecol* 1991;98:789-96.
131. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br.J Obstet.Gynaecol.* 1990;97:734-9.
132. Hallberg L, Nilsson L. DETERMINATION OF MENSTRUAL BLOOD LOSS. *Scand.J Clin.Lab Invest* 1964;16:244-8.
133. Reid PC, Coker A, Coltart R. Assessment of menstrual blood loss using a pictorial chart: a validation study. *BJOG.* 2000;107:320-2.
134. Davies A, Hart R, Magos AL. The excision of uterine fibroids by vaginal myomectomy: a prospective study. *Fertil.Steril.* 1999;71:961-4.
135. Broadbent JAM, Magos AL. Menstrual blood loss after hysteroscopic myomectomy. *Gynaecol Endosc* 1995;4:41-4.
136. Vercellini P, Zaina B, Yaylayan L, Pisacreta A, De Giorgi O, Crosignani PG. Hysteroscopic myomectomy: long-term effects on menstrual pattern and fertility. *Obstet.Gynecol.* 1999;94:341-7.
137. Pelage JP, Le Dref O, Soyer P, Kardache M, Dahan H, Abitbol M *et al.* Fibroid-related menorrhagia: treatment with superselective embolization of the uterine arteries and midterm follow-up. *Radiology* 2000; 215:428-31.
138. Dyer SJ, Abrahams N, Hoffman M, van der Spuy ZM. 'Men leave me as I cannot have children': women's experiences with involuntary childlessness. *Hum Reprod* 2002;17:1663-8.
139. Oddens BJ, den T, I, Nieuwenhuyse H. Psychosocial experiences in women facing fertility problems--a comparative survey. *Hum Reprod* 1999;14:255-61.
140. Stewart EA. Uterine fibroids. *Lancet* 2001;357:293-8.
141. Cote I, Jacobs P, Cumming D. Work loss associated with increased menstrual loss in the United States. *Obstet.Gynecol.* 2002;100:683-7.
142. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
143. Carlson KJ, Miller BA, Fowler FJ, Jr. The Maine Women's Health Study: I. Outcomes of hysterectomy. *Obstet.Gynecol.* 1994;83:556-65.

144. Gimbel H, Zobbe V, Andersen BM, Filtenborg T, Gluud C, Tabor A. Randomised controlled trial of total compared with subtotal hysterectomy with one-year follow up results. *BJOG*. 2003;110:1088-98.
145. Ruta DA, Garratt AM, Chadha YC, Flett GM, Hall MH, Russell IT. Assessment of patients with menorrhagia: how valid is a structured clinical history as a measure of health status? *Qual.Life Res* 1995;4:33-40.
146. Spies JB, Warren EH, Mathias SD, Walsh SM, Roth AR, Pentecost MJ. Uterine fibroid embolization: measurement of health-related quality of life before and after therapy. *J Vasc.Interv.Radiol.* 1999;10:1293-303.
147. Rhodes JC, Kjerulff KH, Langenberg PW, Guzinski GM. Hysterectomy and sexual functioning. *JAMA* 1999;282:1934-41.
148. Hilton P. Trials of surgery for stress incontinence--thoughts on the 'Humpty Dumpty principle'. *BJOG*. 2002;109:1081-8.
149. Fedele L, Parazzini F, Luchini L, Mezzopane R, Tozzi L, Villa L. Recurrence of fibroids after myomectomy: a transvaginal ultrasonographic study. *Hum Reprod* 1995;10:1795-6.
150. Zaloudek CJ, Norris HJ. Mesenchymal tumors of the uterus. In Kurman RJ, ed. *Blaustein's Pathology of the Female Genital Tract*, pp 487-528. Springer-Verlag, New York, 1994.

Appendix 2- Forms

i) Copy of Pinpoint Survey questionnaire

CONSULTANT QUESTIONNAIRE ON THE SURGICAL MANAGEMENT OF UTERINE FIBROIDS

Thank you for making the time to fill out this questionnaire. We would like to find out about current practice for managing women presenting with symptomatic uterine fibroids, and in particular about surgical technique. We appreciate that answering such surveys can be a thankless task, but we feel the information would be of interest to the gynaecological community. It should not take you more than 5 minutes to answer the questions.

Please return to:-

Alex Taylor MB BS MRCOG, Clinical Research Fellow
Adam Magos BSc MD FRCOG, Consultant Gynaecologist
University Department of Obstetrics and Gynaecology,
Royal Free Hospital,
Pond Street,
Hampstead,
London NW3 2QG.

Please answer all the questions by placing a tick in the appropriate box or entering data.

GENERAL QUESTIONS

Q.1 Do you have regular sessions of gynaecological surgery?

☐ Yes ☐ No

Q.2 Year of qualification?

Q.3 Year of membership of RCOG?

Q.4 Where do you mainly work?

☐ Teaching Hospital ☐ District General Hospital ☐ Private Hospital

OPEN MYOMECTOMY

Q.5 How many open myomectomies did you perform in 2001?

☐ None ☐ 1-5 ☐ 6-10 ☐ 11-20 ☐ >20

Q.6 What % required a blood transfusion?

☐ None ☐ <10% ☐ 11-20% ☐ 21-30% ☐ >30%

Q.7A Do you use a specific technique to reduce operative bleeding?

☐ Never ☐ Some of the time ☐ All of the time

Q.7B If you use a specific technique or techniques, please tick the appropriate boxes.

☒ Preop GnRH analogues ☐ Myomectomy clamp ☐ Tourniquets
☐ Vasoconstrictor (eg. vasopressin) ☐ Cutting diathermy on the uterus ☐ Other (please specify)

Q.8 What is the smallest uterus you would manage by open myomectomy?

☐ 8 weeks ☐ 12 weeks ☐ 16 weeks ☐ 20 weeks

Q.9 Would you perform repeat open myomectomy?

☐ No ☐ Only after 1 previous ☐ Even after >1 previous

Q.10 Do you have an upper age limit for doing an open myomectomy?

☐ No ☐ 30 years ☐ 40 years ☐ 50 years ☐ 60 years

Q.11 What preop imaging do you perform in >50% of cases?

If you use more than one, please tick the appropriate

boxes ☐ None ☐ Ultrasound ☐ MRI ☐ CT ☐ Other (please specify)

Please continue overleaf

LAPAROSCOPIC MYOMECTOMY

Q.12 How many laparoscopic myomectomies did you perform in 2001? If none, then proceed to Q19.

☐ None ☐ 1-5 ☐ 6-10 ☐ 11-20 ☐ >20

Q.13 What % required a blood transfusion?

☐ None ☐ 1-10% ☐ 11-20% ☐ 21-30% ☐ >30%

Q.14A Do you use a specific technique to reduce operative bleeding?

☐ Never ☐ Some of the time ☐ All of the time

Q.14B If you use a specific technique or techniques, please tick the appropriate boxes.

☐ Preop GnRH analogues ☐ Tourniquets ☐ Vasoconstrictor (eg.vasopressin)

☐ Cutting Diathermy on the uterus ☐ Other (please specify)

Q.15 What % required conversion to laparotomy?

☐ None ☐ 1-5% ☐ 6-10% ☐ 11-20% ☐ >20%

Q.16 What is the largest uterus you would manage by laparoscopic myomectomy?

☐ 8 weeks ☐ 12 weeks ☐ 16 weeks ☐ 20 weeks

Q.17 Do you have an upper age limit for doing a laparoscopic myomectomy?

☐ No ☐ 30 years ☐ 40 years ☐ 50 years ☐ 60 years

Q.18 What preop imaging do you perform in >50% of cases?

☐ None ☐ ultrasound ☐ MRI ☐ CT ☐ Other (please specify)

HYSTEROSCOPIC MYOMECTOMY

Q.19 How many hysteroscopic myomectomies did you perform in 2001? If none, then proceed to Q23.

☐ None ☐ 1-5 ☐ 6-10 ☐ 11-20 ☐ >20

Q.20 What % required a blood transfusion?

☐ None ☐ 1-10% ☐ 11-20% ☐ 21-30% ☐ >30%

Q.21 What % required conversion to laparotomy?

☐ None ☐ 1-5% ☐ 6-10% ☐ 11-20% ☐ >20%

Q.22 What is the largest uterus you would manage by hysteroscopic myomectomy?

☐ 8 weeks ☐ 12 weeks ☐ 16 weeks ☐ 20 weeks

UTERINE ARTERY EMBOLISATION

Q.23 Do you have access to uterine artery embolisation (UAE) for uterine fibroids?

☐ Yes ☐ No

Q.24 How many women did you refer for UAE in 2001?

☐ None ☐ 1-5 ☐ 6-10 ☐ 11-20 ☐ >20

Q.25 What is the smallest uterus you would refer for uterine artery embolisation?

☐ 8 weeks ☐ 12 weeks ☐ 16 weeks ☐ 20 weeks

Q.26 Would you recommend UAE to someone wanting to conceive?

☐ Yes ☐ No

AND FINALLY

Q.27 Number the following symptoms in the order you feel would be best treated by myomectomy (1=best reason, etc)

☐ Abdominal mass ☐ Pelvic pressure ☐ Infertility ☐ Menorrhagia ☐ Urinary symptoms

Q.28 Respondent number

ii) Menstrual pictogram.

**Reproduced with permission from Prof PMS O'Brien,
Academic dept Obstetrics & Gynaecology,
Keele University**

		DAY OF PERIOD													
TOWEL	TYPE	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Date	BRAND														
	Day time														
	Night time														
	Day time														
	Night time														
	Day time														
	Night time														
	Day time														
	Night time														
	Day time														
	Night time														

Menstrual Pictogram

Please mark which of the pictograms most closely resembles the appearance of each used sanitary towel by placing a tick in the appropriate box. Please note which type/ brand of sanitary towel has been used and whether it was daytime or a night time towel. This should be repeated each time you change your sanitary towel.

Day 1 is the 1st day of your period. There is a separate column for each day of your period.

If you use tampons and pads please mark the tampons on the tampon on the page.

The first column has been filled out as an example.

BLOOD LOST ON SANITARY TOWELS

		DAY OF PERIOD														
TOWEL	TYPE	example	Day 1	day 2	day 3	day 4	day 5	day 6	day 7	day 8	day 9	day 10	day 11	day 12	day 13	day 14
Date	BRAND	Kotex														
	Day time															
	Night time															
	Day time															
	Night time															
	Day time															
	Night time															
	Day time															
	Night time															
	Day time															
	Night time															
	Day time															
	Night time															





Please mark which of the pictures most closely resembles the appearance of each used sanitary towel by placing a tick in the appropriate box. Please note which type/ brand of sanitary towel has been used and whether it was daytime or a night-time towel. This should be repeated each time you change your sanitary towel.

Day 1 is the 1st day of your period. There is a separate column for each day of your period.

If you use tampons and towels please mark the tampons on the tampon page


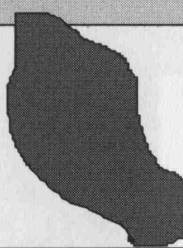
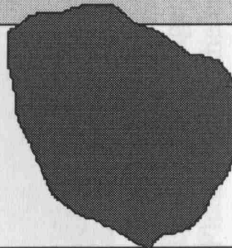
The first column has been filled out as an example

BLOOD LOST ON TAMPONS

TAMPON	DATE	TYPE	example	DAY OF PERIOD															
				day 1	Day 2	day 3	day 4	day 5	day 6	day 7	day 8	day 9	day 10	day 11	day 12	day 13	day 14		
		BRAND	Tampax																
		Regular																	
		Super																	
		Super Plus																	
		Regular																	
		Super																	
		Super Plus																	
		Regular																	
		Super																	
		Super Plus																	
		Regular																	
		Super																	
		Super Plus																	

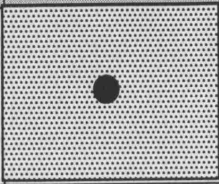
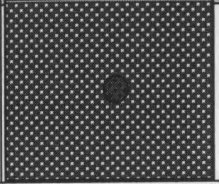
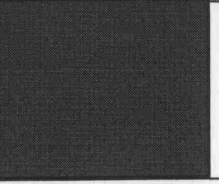
Please mark which of the pictures most closely resembles the appearance of each used tampon by placing a tick in the appropriate box. Please note which type of tampon has been used and whether it was regular, super or super plus. This should be repeated each time you change your tampon. **Day 1 is the 1st day of your period. There is a separate column for each day of your period. The first column has been filled out as an example.**

BLOOD LOST AS CLOTS DURING YOUR PERIOD

CLOTS	example	DAY OF PERIOD													
		day 1	day 2	day 3	day 4	day 5	day 6	day 7	day 8	day 9	day 10	day 11	day 12	day 13	day 14
															
															
															

Please mark the presence and size of clots using the size of the pictures to guide you. A tick should be placed in the appropriate box each time you lose a blood clot. Day 1 is the first day of your period. There is a separate column for each day of your period. **The first column has been filled out as an example.**

BLOOD LOSS IN THE TOILET WHEN CHANGING SANITARY WEAR

TOILET	example	DAY OF PERIOD													
		day 1	day 2	day 3	day 4	day 5	day 6	day 7	day 8	day 9	day 10	day 11	day 12	day 13	day 14
															
															
	I														

Before you change your sanitary wear please place a 2p piece at the bottom of your toilet.

Please look at the colour of the water *before* you put any paper into the toilet

Which of these pictures are most like the colour of the water and how clearly can you see the coin. If there are any clots please mark them on the 'clot chart'.

If you are using a lavatory without a coin in it please estimate which colour is closest to the colour of the water.

Day 1 is the 1st day of your period. There is a separate column for each day of your period

The first column has been filled out as an example.

TAMPON	TYPE	Score in ml
DATE	BRAND	
	Regular	0.5
	Super	1.0
	Super Plus	1.0
	Regular	1.0
	Super	1.5
	Super Plus	2.0
	Regular	1.5
	Super	3.0
	Super Plus	4.0
	Regular	4.0
	Super	8.0
	Super Plus	12.0

TOWELS	TYPE	Score
	Day time	1 ml
	Night time	1 ml
	Day time	2 ml
	Night time	3 ml
	Day time	3 ml
	Night time	6 ml
	Day time	4 ml
	Night time	10 ml
	Day time	5 ml
	Night time	15 ml

CLOTS	Score
	1 ml
	3 ml
	5 ml

TOILETS	Score
	1 ml
	3 ml
	5 ml

iii) Reproduced with permission by The Cardiovascular and
Interventional Radiology and Education Foundation (CIRREF)

Pt. Initials: _____

Pt. ID: _____

Date: _____

UTERINE FIBROID SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE
QUESTIONNAIRE (UFS-QOL)

Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If a question does not apply to you, please mark "not at all" as a response.

During the previous 3 months, how distressed were you by...	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
2. Passing blood clots during your menstrual period	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
3. Fluctuation in the duration of your menstrual period compared to your previous cycle	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
4. Fluctuation in the length of your monthly cycle compared to your previous cycles	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
5. Feeling tightness or pressure in your pelvic area	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
6. Frequent urination during the daytime hours	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
7. Frequent nighttime urination	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
8. Feeling fatigued	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

The following questions ask about your feelings and experiences regarding the impact of uterine fibroid symptoms on your life. Please consider each question as it relates to your experiences with uterine fibroids during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If the question does not apply to you, please check "none of the time" as your option.

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9. Made you feel anxious about the unpredictable onset or duration of your periods?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Made you anxious about traveling?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Interfered with your physical activities?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Caused you to feel tired or worn out?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Made you decrease the amount of time you spent on exercise or other physical activities?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Made you feel as if you are not in control of your life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Made you concerned about soiling underclothes?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Made you feel less productive?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Caused you to feel drowsy or sleepy during the day?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Made you feel self-conscious of weight gain?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. Made you feel that it was difficult to carry out your usual activities?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. Interfered with your social activities?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. Made you feel conscious about the size and appearance of your stomach?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Made you concerned about soiling bed linen?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Thank you!

For the statistical analysis, if < 50% of the items were answered, the scale would be regarded as the majority of the items were not answered correctly for the research study. If > 50% of the items were answered, the scale would be considered as the majority were answered correctly. If a reference value is necessary, the 50% value would be used.

UFS-QoL Scoring Manual

To calculate a symptom score for symptom severity, create a summed score from the items listed below and then use the formula below the table to transform the value. This will provide symptom scores where higher score values are indicative of greater symptom severity or bother and lower scores will indicate minimal symptom severity (high scores = bad).

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Symptom Severity	Sum 1 – 8	8, 40	32

Transformation for Symptom Severity raw scores ONLY:

$$\text{Transformed Score} = \frac{(\text{Actual raw score} - \text{lowest possible raw score})}{\text{Possible raw score range}} \times 100$$

For the HRQL subscales (concern, activities, energy/mood, control, self-conscious, and sexual function), create summed scores of the items listed below for each individual subscale. To calculate the HRQL total score, sum the value of each individual subscale (do not sum individual items). Use the formula below the table to transform all values. Higher scores will be indicative of better HRQL (high = good).

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Concern	9+15+22+28+32	5, 25	20
Activities	10+11+13+19+20+27+29	7, 35	28
Energy/mood	12+17+23+24+25+31+35	7, 35	28
Control	14+16+26+30+34	5, 25	20
Self-conscious	18+21+33	3, 15	12
Sexual function	36+37	2, 10	8
HRQL TOTAL	Sum of 6 Subscale Scores	29, 145	116

Formula for transformation of HRQL raw scores ONLY:

$$\text{Transformed Score} = \frac{(\text{Highest possible score} - \text{Actual raw score})}{\text{Possible raw score range}} \times 100$$

Missing Items

For the subscale analyses, if < 50% of the scale items are missing, the scale should be retained with the mean scale score of the items present used to impute a score for the missing items. If ≥ 50% of the items are missing, no scale score should be calculated, the subscale score should be considered missing. If a subscale score is missing, the HRQL total cannot be calculated.

Appendix 3: CD (including movies and Excel files containing original data for the studies

